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Drug Evaluation: Buprenorphine for Pain

Date of Review: February 2023
Generic Name: Buprenorphine, buprenorphine/naloxone
PDL Classes: Opioid & Alcohol Substance Use Disorders; Long-acting Opioids

End Date of Literature Search: 11/11/2022
Brand Name: multiple

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Review:
The purpose of this review is to establish the place in therapy of buprenorphine for the management of acute and chronic non-cancer pain relative to other opioid therapy. Additionally, this evaluation will describe the risk for overdose, misuse, abuse, diversion, and dependence of buprenorphine relative to other opioids, which may affect coverage decisions.

Plain Language Summary: Is buprenorphine better at treating non-cancer pain or safer than other opioids?

- Opioids are a medicine used to treat severe pain. Opioids are not better at improving pain or function compared to other types of non-opioid pain medicines but they do have greater risk of overdose, death, and addiction. Opioid medicine is only recommended when other pain medicines have been tried and do not control pain well enough.
- Long-acting opioid medicines are designed to release medicine in the body over an extended period of time, but they have a higher risk of overdose and death compared to short-acting opioid medicines. The U.S. Food and Drug Administration has approved long-acting opioid medicines only when short-acting opioid medicines have been tried and do not control pain well enough. Several national guidelines also recommend short-acting opioids over long-acting opioids for most people.
- Buprenorphine is an opioid that works differently than other opioid medicines. Most buprenorphine is prescribed for opioid use disorder, but some long-acting buprenorphine is designed to help manage chronic pain. Very little is known about whether buprenorphine controls pain better or is safer than other opioid medicines. A few very short studies (with durations of less than 6 months) do not show that buprenorphine is better at treating pain or safer than other opioids for pain treatment. The U.S. Food and Drug Administration has the same safety cautions and warnings for buprenorphine as other opioids.
- People who already take an opioid medicine may have serious withdrawal symptoms if they abruptly stop taking the medicine (symptoms may be anxiety, pain, sleep problems, upset stomach, and craving opioids). Prescribers and their patients should work together to find a therapy that will decrease risks of opioid therapy and treat the patient's pain. Switching from other opioids to buprenorphine may be one option for patients and providers to consider, but we do not yet know if buprenorphine decreases risk of overdose or addiction when it is used to manage chronic pain.

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- The Oregon Health Plan covers buprenorphine for opioid use disorder. Providers must explain to the Oregon Health Plan why therapy is needed if they prescribe a long-acting buprenorphine medicine for pain or if they prescribe more than 24 mg per day of buprenorphine for opioid use disorder. This process is called prior authorization. The goal of prior authorization is to make sure these medicines are used safely.
- We recommend that the Oregon Health Plan cover long-acting opioid medicines only when other pain medicines including short-acting opioids do not control pain well enough.

Research Questions:

1. What is the comparative efficacy or effectiveness of buprenorphine compared to other opioids in reducing acute or chronic non-cancer pain and improving functional outcomes in adult and pediatric patients?
2. What is the evidence for comparative harms, safety concerns (cognitive impairment, sedation, and respiratory depression), unintended effects (euphoria and withdrawal cravings) and risk of misuse, abuse, dependence, and diversion of buprenorphine compared to other opioids in adult and pediatric patients treated for chronic non-cancer pain?
3. Are there subpopulations of patients based on age (e.g., pediatric patients), race, comorbidities (e.g., renal or hepatic impairment, history of opioid abuse, alcohol dependence, mental health conditions, or pre-initiation functional level), concomitant drug therapies (benzodiazepines or marijuana use), or socioeconomic status (e.g., Medicaid, housing status) who may be at a higher risk for harms or risk for misuse, abuse, dependence, and diversion with buprenorphine use?

Conclusions:

- General recommendations for opioid therapy
    - Guidelines from the Department of Defense and Department of Veterans Affairs (VA/DOD) and National Institute for Health and Care Excellence (NICE) continue to recommend against initiation of opioids (including buprenorphine) for chronic pain.[1-3] In patients with chronic pain, opioids are associated with a small improvement in pain and function compared to placebo. Current evidence does not demonstrate any clinical benefit in efficacy of opioids (as a class of medications) compared to alternative non-opioid analgesics for treatment of chronic pain.[4] Long-term opioid therapy has been associated with serious risks including increased risk of overdose and development of substance use disorder. [4] Recent guidelines typically recommend initiation of opioids only when:[1,5,6]
        - alternative therapies have been maximized,
        - potential benefits outweigh risks,
        - clinician and patient have discussed realistic benefits and risks of treatment and established goals of therapy, and
        - there is an established plan to reassess therapy and discontinue treatment if benefit is not established.
    - For acute pain, non-opioid therapy (including nonpharmacological treatment) should be maximized before starting an opioid.[6]
    - In patients with chronic pain already established on opioid therapy, current guidelines all recommend careful reassessment of risks and benefits including shared decision making for discontinuation of opioids or risk mitigation for continued therapy.[1,3,5,6] Withdrawal symptoms have been documented with abrupt discontinuation of opioids (including buprenorphine) during post-marketing studies.
    - Long-acting, scheduled opioids generally result in exposure to a higher daily dose compared to short-acting, as-needed opioids and are associated with increased risk of overdose and death (low quality evidence).[4,6] The Department of Defense and Department of Veterans Affairs (VA/DOD) and Centers for Disease Control (CDC) guidelines recommend against use of long-acting opioid formulations for acute pain, as an as-needed medication, or when initiating opioid therapy for chronic pain.[1,6]

- Buprenorphine efficacy
    - There is moderate quality from direct and indirect evidence that buprenorphine provides similar reduction in pain intensity with short-term use (less than 6 months) compared to other opioids for patients with chronic pain. There is insufficient evidence to compare buprenorphine to other opioids for acute pain or for chronic pain beyond 6 months.[4] Data is significantly limited by lack of long-term studies, and there is low quality evidence that efficacy of opioids, in general, may attenuate with long-term use (over 3 to 6 months).[6]
- Buprenorphine safety
    - There is low quality evidence that buprenorphine is not safer than other opioids for treatment of chronic pain.[1,6] Literature referencing improved safety of buprenorphine primarily references assumed benefits based on the mechanism of action. However, data from well-controlled, comparative trials are lacking, and indirect comparisons from short-term trials show similar rates of common adverse events, serious adverse events, and withdrawals due to adverse events compared to other opioids. Regulatory agencies (including the U.S. Food and Drug Administration [FDA]) recommend similar precautions for buprenorphine as other opioids. All formulations have warnings for risks for abuse, misuse, addiction, respiratory depression, overdose, neonatal opioid withdrawal syndrome, withdrawal symptoms, adrenal insufficiency, and hepatic adverse events.
    - Most guidelines do not recommend buprenorphine over other opioids. However, the Department of Veterans Affairs and Department of Defense (VA/DOD) 2022 guideline for the treatment of chronic pain includes a suggestion for use of buprenorphine instead of full agonist opioids for patients prescribed daily opioids for chronic pain (weak recommendation for therapy).[1] The systematic literature review supporting this recommendation found low quality evidence that buprenorphine was equally effective at controlling pain compared to other opioids and insufficient evidence evaluating safety of buprenorphine compared to other opioids. In the absence of any evidence, guideline authors note that the theoretical safety profile of buprenorphine based on the mechanism of action as a partial agonist and status as a schedule III substance may decrease long-term risks compared to full opioid agonists (which are classified as schedule II substances and have known overdose risks).[1] However, benefits of buprenorphine should be weighed against the lack of evidence for improved safety compared to other opioids. Buprenorphine should be used with caution, especially in patients who are opioid-naïve, patients who are opioid-experienced with low or intermittent dosing, and patients that have concomitant use of other central nervous system depressants.[1] Most studies have not evaluated buprenorphine in these populations, and labeling for buprenorphine includes precautions for overdose in all of these groups.[1]
- Subgroups
    - Very little evidence compares buprenorphine to other opioids in specific groups of people. Studies that evaluate specific groups of patients who may be at increased risk of harms from opioids are based on opioids as a drug class and do not compare individual opioids. There are no validated tools which can accurately identify patients who may be at risk for opioid overdose, addiction, abuse, or misuse.[4,6]
    - There is low quality evidence that use of opioids in combination with benzodiazepines and gabapentinoids increases risk of overdose.[4,6] There is insufficient evidence that buprenorphine differs from other opioids when combined with other sedating agents.
    - Higher doses of opioids are associated with increased risk of overdose, mortality, abuse, dependence, addiction, falls and major trauma, injury from traffic accidents, and endocrine-related adverse events compared to lower doses (low quality evidence).[4,6] However, there is no minimum dose threshold for which there is no overdose risk.[6]
    - There is insufficient evidence that long-acting buprenorphine is associated with less risk for overdose compared to other long-acting opioids. Adverse events were similar when buprenorphine was compared to other long-acting opioids based on low quality evidence from short-term studies (follow-up of 6 months or less).[4,6]
    - There is insufficient evidence to compare buprenorphine to other opioids for pain in treatment-naïve patients. Labeling for buprenorphine includes a warning for risk of overdose in this population, and long-acting formulations are only recommended if immediate-release opioids are inadequate.[7-10] Trials evaluating buprenorphine for pain have primarily enrolled patients with a prior history of opioid use.

- There is insufficient evidence to know whether buprenorphine is safer or more effective than other opioids when used for pain in specific patient demographics or in patients with specific comorbidities.[4] Opioid overdose may be more frequent in younger people and in patients with comorbid opioid use disorder (OUD).[1] In patients with comorbid OUD, current guidelines recommend patients be treated with appropriate medication assisted treatment (MAT) (irrespective of presence or absence of pain).[1,6] Recommended first-line treatments for MAT include buprenorphine or methadone. There is low quality evidence that both buprenorphine and methadone provide similar improvements in pain intensity, physical functioning, and adverse events in patients with OUD.[11] Most trials evaluating efficacy and safety of buprenorphine for pain excluded patients with behavioral health issues including substance use disorders.

Recommendations:

- No PDL changes are recommended for buprenorphine based on the clinical evidence.
- Because long-acting opioid formulations are associated with increased risk of overdose and death compared to short-acting opioids, update PA criteria to limit use of all long-acting opioids to patients who have inadequate pain relief with short-acting opioids (see **Appendix 5**).

Summary of Current Policy:

- In Oregon fee-for-service (FFS) Medicaid, various buprenorphine formulations are categorized by their FDA-approved indication.
- Opioid products that are indicated for OUD are available without prior authorization. These include sublingual buprenorphine formulations, provider administered oral methadone, and subcutaneous buprenorphine injections.
- Prior authorization is required for all long-acting opioid formulations including transdermal buprenorphine patches and buccal films.
- Acute use of short-acting opioids (up to 7 days) does not require prior authorization. Providers can prescribe up to 2 prescriptions of short-acting opioids every 90 days without PA, and can request longer-term opioid therapy through the prior authorization process.
- Long-term opioid treatment for both short-acting or long-acting formulations can be approved when benefits outweigh potential risks and with appropriate ongoing monitoring.

Background:

Pain management is an important aspect for a variety of acute and chronic conditions. Both non-pharmacologic treatments (such as rehabilitative therapy, chiropractic or osteopathic manipulation, and acupuncture) and pharmaceutical analgesics play an important role in management of pain. Prescription analgesics commonly prescribed for pain management include non-steroidal anti-inflammatory agents (NSAIDs), acetaminophen, topical analgesics, muscle relaxants, and opioids. Evidence supporting specific interventions varies depending on the condition, but current guidelines routinely recommend non-opioid pharmaceuticals and non-pharmacologic treatments for the initial treatment of acute or chronic pain. Most guidelines, medical societies, and public health agencies have recently recommended against routinely prescribing opioids due to increasing evidence of harms reported in observational and epidemiologic studies. These harms include increased mortality, development of opioid use disorder, overdose, sexual dysfunction, fractures, myocardial infarction, constipation, and sleep-disordered breathing.[1] Opioids have also been implicated in impaired cognitive function and development of new onset depression.[1] These factors have resulted in a decreased dispensing rate of prescription opioids from practitioners over time. However, harms have also been documented with rapid discontinuation or tapering of prescription opioids, including risk of suicidal ideation, suicide, and overdose following opioid discontinuation.[1] And, despite a decrease in prescription opioid use, death due to drug overdoses have continued to increase in recent years.[1] In 2019, over 70% of the 71,000 deaths the United States due to drug overdose involved an opioid.[1] The number of people who die from an accidental opioid overdose has also surpassed deaths from motor vehicle accidents.[1] The COVID-19 pandemic has only exacerbated this trend, with preliminary CDC data showing an increase of nearly 30% in drug

overdoses from 2019 to 2020.[1,12] Similar trends have been observed in Oregon. Provisional data indicate that overdose deaths of all types has increased by more than 76% from 2011 to 2021, with overdose deaths specifically related to fentanyl and other synthetic opioids increasing by 83% from 2020 to 2021.[13] Fentanyl or fentanyl analogues, including illicitly manufactured derivatives, were the most common type of opioid identified (present in approximately 48% of all overdose deaths in 2021).[13]

The opioid epidemic started in predominantly white communities; but in recent years, literature has documented varying impacts across ethnic groups. For example, recent epidemiologic trends demonstrate that overdose deaths increased disproportionally among non-Hispanic Black individuals compared to other racial and ethnic groups from 2018 to 2019. Historically, patients from racial and ethnic groups that have experienced historical and current discrimination are also less likely to receive adequate care for pain.[1] Black patients were also less likely to be referred to a pain specialist, less likely to receive prescription opioids, and more likely to be discontinued from opioids in the presence of positive test for illicit opioid use compared to white patients.[1] These racial disparities highlight important differences in care that may impact access to services and outcomes with treatment.

While illicit opioids (such as heroin and non-prescription fentanyl) have been implicated in increased death rates over time, the American Medical Association has reported that nearly half of all heroin users started with an addiction to a prescribed opioid medication before switching to heroin due to ease of access.[1] Thus, there is a need for prescribers to carefully consider risks and benefits before initiating opioid therapy, engage patients in shared decisions regarding continuation of opioids, and to address management of pain and risk mitigation based on individual patient circumstances.

Improvement in pain severity or intensity is one of the most commonly reported efficacy outcomes for pain studies. However, outcomes evaluating the impact of treatment on disability, function, and quality of life are equally important. Pain intensity measurements used in clinical trials include the visual analog scale (VAS; scale, 0-100 or 0-10) and numerical rating scale (NRS; scale, 0-10).[14] The NRS and VAS are highly correlated and can be interpreted equally. For acute pain, the minimum clinically important difference (MCID) in the 11-point VAS is 1.4 (95% CI, 1.2 to 1.6).[15] Similar MCID values have been shown with 100-point scales.[16] The proposed MCID thresholds for chronic pain and low back pain are about 2 points on the 0 to 10-point scale or 20 points on the 0 to 100-point scale.[14] The impact of opioids on disability is also frequently studied in clinical trials of low back pain. Measurements commonly used include the Oswestry Disability Index scores (range, 0-100) and the Roland-Morris Disability Questionnaire (RMDQ) scores (range, 0-24).[14] The Oswestry Disability Index and RMDQ tools are also highly correlated and share similar properties.[14] Similarly, a 10-point difference in 0-100 scales for chronic disability is considered a “minimal” difference and 20-point differences are considered to be “clinically important”.[14] The Brief Pain Inventory (BPI) is widely used in pain specialty and research settings, but is impractical for clinicians caring for patients in the office due to instrument length and scoring complexity.[17] An ultra-brief pain measure derived from the BPI was developed and validated in patients with chronic pain in 2009.[17] This 3-item scale assesses pain intensity (P), interference with enjoyment of life (E), and interference with general activity (G) using a VAS ranging from 0 (no pain/no interference) to 10 (pain as bad as you imagine/complete interference).[17] The PEG scale proved to be a reliable and valid measure of pain among primary care patients with chronic musculoskeletal pain and diverse Veterans Affairs (VA) ambulatory patients.[17] The PEG was also comparable to the BPI in terms of responsiveness to between patients with and without pain improvement at 6 months.[17] For these reasons, the PEG scale was added to the OHP clinical PA criteria for opioids in 2016. Important safety outcomes include common adverse events, adverse events resulting in discontinuation of treatment, development of opioid use disorder, addiction, misuse or abuse, overdose, and death.

The available literature directly evaluating comparative data for opioids is small, particularly in the setting of chronic pain. Most randomized controlled trials (RCTs) evaluating opioid therapy use a placebo comparator, and studies evaluating efficacy and safety of opioids rarely exceed 6 months.[4] Opioids can be divided into several categories based on their mechanism of action and include full mu opioid agonists (e.g., morphine, hydrocodone, hydromorphone, oxycodone,

fentanyl, and methadone), partial mu opioid agonists (e.g., buprenorphine), and opioid agonists which target additional receptors (e.g., tramadol, tapentadol). Short-term use of opioids consistently results in greater analgesia than with few serious adverse events.[4,6,18] However, long-term observational studies of opioid therapy have documented risks for increased mortality, development of opioid use disorder, overdose, sexual dysfunction, fractures, myocardial infarction, constipation, and sleep-disordered breathing.[1,4,6] Therefore, there is need to identify safer options for the treatment of chronic pain. The OHP Pharmacy and Therapeutics (P&T) Committee previously evaluated the efficacy and safety of tramadol compared to other opioids, and there is current interest in whether buprenorphine differs from other opioids.

Buprenorphine is a schedule III-controlled substance and is available in a variety of formulations. Formulations of buprenorphine which are FDA-approved for treatment of OUD include subcutaneous injections (SUBLOCADE) and sublingual films or tablets with or without naloxone (SUBOXONE, ZUBSOLV, SUBUTEX). Buprenorphine formulations which are indicated for treatment of severe pain include buccal films (BELBUCA), transdermal patches (BUTRANS), and intramuscular or intravenous injections (BUPRENEX). In Oregon fee-for-service (FFS) Medicaid, various buprenorphine formulations are categorized by their FDA-approved indication. Therefore, transdermal patches and buccal films are categorized as long-acting opioids and subject to clinical prior authorization (PA) criteria for opioids. Subcutaneous injections and sublingual formulations are categorized as MAT for OUD and are available without PA. The preferred drug list (PDL) and clinical PA criteria do not apply to intramuscular and intravenous injections as these are expected to be administered by healthcare providers to manage acute pain. Warnings and precautions included in the FDA labeling for long-acting buprenorphine formulations are consistent with other opioids.[9,10] Boxed warnings include risk of addiction, abuse, misuse, overdose, respiratory depression, risks with concomitant sedatives, accidental exposure, and neonatal abstinence syndrome.[9,10] Other precautions include risk for severe hypotension, withdrawal symptoms, and respiratory depression in patients with pulmonary disease, cachexia, elderly, increased intracranial pressure, or brain injury.[9,10] Use should be avoided in patients with gastrointestinal obstruction or adrenal insufficiency and use should be reserved for when alternatives (including IR opioids) are inadequate or contraindicated.[9,10] Labeling for buprenorphine formulations indicated for OUD have similar precautions for adverse events including addiction, abuse, misuse, respiratory depression, withdrawal, and neonatal abstinence syndrome.[7,8,19]

Switching between opioid products typically requires careful monitoring for withdrawal symptoms, breakthrough pain, respiratory depression, and overdose. Many protocols describing transition from other opioids to buprenorphine require patients to exhibit mild withdrawal symptoms before initiation of buprenorphine therapy in order to avoid risk of overdose based on inter-patient variability in opioid potency.[9,20] FDA labeling for buccal buprenorphine recommends providers taper a patient's current opioid to less than 30 MME before initiating treatment.[9] Labeling for transdermal buprenorphine recommends other scheduled opioids be discontinued at the time of the first transdermal dose.[10] A few recent protocols have described a strategy of administering very low doses of sublingual buprenorphine (i.e., microdosing) before discontinuation of current opioid therapy in order to avoid withdrawal symptoms when transitioning from other opioids to buprenorphine.[21-24] However, much of the evidence is for this method is based on case reports and case series involving fewer than 10 patients.[21-24]

Because buprenorphine is a partial mu opioid agonist, it may have potential advantages compared to full opioid agonists. Pharmacokinetic properties of buprenorphine are listed in **Table 1**. Potential advantages of buprenorphine cited in the literature have included ceiling effect for respiratory depression, improved safety in elderly and renal disease due to favorable metabolic processes, increased efficacy for neuropathic pain, less development of tolerance, lack of hyperanalgesic effect, and antidepressant effects.[25] Potential disadvantages of buprenorphine include high affinity for the opioid receptor, which may limit the utility of naloxone rescue for reversal of an overdose.[9,10] However, these claims are generally based on assumptions about mechanism and pharmacology, and not well designed prospective studies. Additionally, several publications which cite advantages of buprenorphine also note manufacturer funding.[25] This review will evaluate available literature examining efficacy and safety of buprenorphine compared to other opioids.

Table 1. Buprenorphine Pharmacology and Pharmacokinetic Properties.[26,27]

Parameter	Sublingual tablet/film	Transdermal patch	Buccal tablet	SC Injection
Absorption	Variable between patients but variability within each individual patient is low. Ingestion of liquids decreases systemic exposure by 23%-59% (dependent on pH of the liquid).	Application of a heating pad onto the transdermal system may increase blood concentrations of buprenorphine by 26-55%.	Variable between patients but variability within each individual patient is low. Ingestion of liquids decreases systemic exposure by 23%-37% (dependent on pH of the liquid)	Precipitation following injection results in a solid depot which will gradually release buprenorphine via diffusion and biodegradation of the depot.
Bioavailability (relative to IV)	Variable for different products. There is a relative increase in exposure with film compared to tablets. Buprenorphine concentration for ZUBSOLV® 5.7 mg is roughly equivalent to SUBOXONE® 8 mg Buprenorphine: ~29%	15%	46-65%	Not reported
Half-Life (adults)	Buprenorphine: ~37 hours SUBOXONE®: 24-42 hours BUNAVAIL®: 16.4-27.5 hours	~26 hours	27.6 ± 11.2 hours	43 to 60 days
Mechanism of Action	high-affinity binding to mu opioid receptors in the CNS which results in analgesic effects; displays partial mu agonist effects and weak kappa antagonist activity			
Distribution and Protein Binding	CSF concentrations are ~15-20% of plasma concentrations; Vd: 430 liters Protein binding: ~96% primarily to alpha- and beta globulin			
Metabolism	Primarily hepatic via N-dealkylation by CYP3A4 to norbuprenorphine, an active metabolite. Inhibitor of CYP2D6 and CYP3A4.			
Elimination	~70% via feces (33% as unchanged drug; 21% as norbuprenorphine) 27-30% via urine (9.4% as conjugated drug; 11% as conjugated norbuprenorphine)			

Abbreviations: CNS = central nervous system; CSF = cerebrospinal fluid; IV = intravenous; mg = milligram; Vd = volume of distribution

Methods:

A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

Multiple high quality systematic reviews have been published in recent years which evaluate evidence of opioids for acute and chronic pain. For many of these reviews, evidence for opioids is presented as a class of drugs compared to placebo and the efficacy and safety of individual agents is not evaluated. The evidence presented in this review will focus primarily on evidence that evaluates comparative data of buprenorphine to other opioids for the management of acute and chronic non-cancer pain. Evidence that evaluates efficacy and safety opioids as a class of medications will not be discussed in detail. Both buprenorphine and methadone are recommended as first-line treatment options for MAT in patients with OUD. Evidence supporting management of buprenorphine for OUD will not be included in this review.

A systematic review from AHRQ published in 2020 and updated in March 2022 evaluated evidence of opioids for chronic pain.[4] The review specifically evaluated evidence regarding effectiveness based on type of opioid (pure agonist, partial agonist, or opioids with a mixed mechanism). For pain relief, there was moderate quality evidence of no difference in efficacy outcomes between buprenorphine and pure opioid agonists. Direct comparative evidence was limited to 3 RCTs, and subgroup analyses from placebo-controlled data were used to supplement conclusions. Two RCTs (n=415) directly compared transdermal buprenorphine to tramadol with no difference in pain intensity, sleep, discontinuation due to adverse events, or specific adverse events. One small RCT (n=46) compared buprenorphine to transdermal fentanyl and found no difference in pain intensity, function, mood or adverse events.[4] Placebo-controlled data were available from 38 trials of pure opioid agonists and 8 trials of buprenorphine (5 evaluated transdermal patch and 2 evaluated buccal formulation) and 16 trials evaluated mixed opioids (tramadol or tapentadol).[4] Subgroup analyses of the placebo-controlled data showed no interactions between type of opioid (full, partial, or mixed) and effects on pain, function, pain response, SF-36 health status, sleep or depression. Similarly, no difference in short-term harms based on the mechanism of action was found.[4] Compared to placebo, opioids of all types were associated with increased rates of study participant discontinuation due to adverse events (number needed to harm [NNH] of 10; moderate quality evidence) and common adverse events, but were not associated with serious adverse events in short-term RCTs.[4] Adverse events more common than placebo included somnolence (NNH 11), nausea (NNH 7), vomiting (NNH 14), constipation (NNH 7), dizziness (NNH 12) and pruritus (NNH 14). Pruritus was only adverse event which demonstrated a statistical difference based on type of opioid with higher risk associated with pure agonists and mixed mechanism opioids compared to buprenorphine.[4] However, the analysis was limited to 3 trials of buprenorphine. Pooled analyses for each type of opioid are presented in **Table 2** for each outcome.

Table 2. Subgroup analysis for efficacy outcomes compared to placebo based on opioid type[4]

Outcome	Overall	Pure agonists	Partial agonists	Mixed mechanism	p-value for interaction
Pain response*; RR (95% CI)	1.35 (1.24 to 1.48)	1.39 (1.24 to 1.60)	1.45 (1.20 to 1.76)	1.27 (1.10 to 1.51)	0.47
Pain; MD (95% CI)	-0.79 (-0.93 to -0.67)	-0.82 (-1.04 to -0.63)	-0.71 (-0.90 to -0.49)	-0.81 (-1.04 to -0.60)	0.85
Function; SMD (95% CI)	-0.22 (-0.28 to -0.16)	-0.20 (-0.30 to -0.10)	-0.25 (-0.46 to -0.03)	-0.22 (-0.30 to -0.15)	0.72
SF-36 physical function; MD (95% CI)	1.64 (1.10, 2.17)	1.82 (0.48 to 2.96)	2.20 (-0.82 to 5.13)	1.54 (0.82 to 2.15)	0.80
Sleep; SMD (95% CI)	-0.25 (-0.32 to -0.19)	-0.26 (-0.40 to -0.17)	-0.28 (-0.45 to -0.13)	-0.23 (-0.36 to -0.15)	0.92
Depression; SMD (95% CI)	0.00 (-0.22 to 0.18)	-0.01 (-0.19 to 0.20)	0.31 (0.02 to 0.60)	-0.35 (-1.03 to 0.13)	0.14
Discontinuation due to AEs; RR (95% CI)	2.25 (1.86 to 2.73)	2.06 (1.57 to 2.75)	2.28 (1.08 to 5.01)	2.55 (1.93 to 3.36)	0.64
Serious Adverse Events; RR (95% CI)	1.23 (0.88 to 1.74)	1.42 (1.01 to 2.01)	1.27 (0.68 to 2.38)	0.95 (0.39 to 2.34)	0.48
Somnolence; RR (95% CI)	2.97 (2.44 to 3.66)	2.72 (2.01 to 3.78)	2.80 (1.47 to 4.95)	3.40 (2.60 to 4.69)	0.43
Nausea; RR (95% CI)	2.46 (2.17 to 2.80)	2.29 (1.90 to 2.74)	1.99 (1.29 to 3.19)	2.97 (2.50 to 3.54)	0.06

Vomiting; RR (95% CI)	3.57 (2.98 to 4.34)	3.17 (2.36 to 4.31)	3.65 (2.34 to 5.86)	4.19 (3.22 to 5.68)	0.32
Constipation; RR (95% CI)	3.38 (2.96 to 3.92)	3.21 (2.74 to 3.87)	2.53 (1.56 to 4.55)	3.82 (3.20 to 4.89)	0.10
Dizziness; RR (95% CI)	2.66 (2.37 to 2.99)	2.43 (1.92 to 3.08)	2.85 (1.99 to 4.30)	2.80 (2.39 to 3.28)	0.48
Headache; RR (95% CI)	1.06 (0.95 to 1.17)	0.96 (0.79 to 1.14)	1.23 (0.87 to 1.67)	1.09 (0.94 to 1.29)	0.31
Pruritus; RR (95% CI)	3.51 (2.47 to 5.16)	4.02 (2.44 to 6.48)	1.18 (0.80 to 1.91)	4.77 (3.01 to 7.95)	0.02[+]

Abbreviations: AE = adverse events; CI = confidence interval; MD = mean difference; RR = relative risk; SF-36 = short-form 36; SMD = standard mean difference.
*Commonly defined as >30% improvement from baseline; [+]statistically significant difference between groups

Because data from RCTs were not powered or designed to evaluate long-term harms (e.g., opioid use disorder, dependence, overdose), evidence on serious long-term adverse events was derived primarily from observational studies.[4] Several large observational studies provided low quality evidence that opioids are generally associated with increased risk for abuse, dependence, addiction, overdose, mortality, myocardial infarction, fracture, falls, and endocrine dysfunction (erectile dysfunction, female reproductive dysfunction, androgen deficiency).[4] Based on observational studies, opioids were also generally associated with increased risk of overdose in combination with a benzodiazepine (especially with short-term use) or gabapentinoids (particularly at higher gabapentinoid doses) based on low quality evidence.[4] Higher doses of opioid were also generally associated with increased risk of cardiovascular events, road trauma events (when limited to drivers), endocrine dysfunction, mortality, overdose, abuse, dependence or addiction compared to lower doses (based on low quality evidence).[4] In some studies, risk for falls and fractures was highest at the start of therapy and decreased with longer-term use.[4]

Evidence related to the type of opioid and risk for OUD, overdose, fracture, falls or cardiovascular events was very limited.[4] Only one study reported data on buprenorphine compared to other opioids. An observational study of 9,500 patients identified an increased risk of hip fracture for patients prescribed opioids (age adjusted incidence 3.47 vs. 1.94 per 100 person-years, hazard ratio [HR] 1.96, 95% CI, 1.27 to 3.02).[4] Risk was not statistically significant for patients prescribed codeine or dihydrocodeine (HR 1.70, 95% CI, 0.89 to 3.26) but was statistically significant for patients prescribed buprenorphine (HR 1.98, 95% CI, 1.33 to 2.95) and other full opioid agonists (HR 2.72, 95% CI, 1.25 to 5.93) compared to no opioid use.[4] Several studies also evaluated risk of short-acting opioids compared to long-acting opioids. In a single small study, transdermal buprenorphine 20 mcg/hr was associated with increased rate of discontinuation due to adverse events compared to short-acting oxycodone 40 mg/day (13% vs. 7%, relative risk [RR] 1.82, 95% CI, 1.02 to 3.26), but specific adverse events were similar between groups and data were limited by the enriched study design.[4] A large cohort study (n=840,606) found that long-acting opioids were associated with increased risk of overdose compared to short-acting opioids (HR 2.33, 95% CI, 1.26 to 4.32). Risk was highest with initiation (HR 5.2, 95% CI, 1.89 to 14.72 at ≤14 days) and decreased with longer duration of exposure (HR 1.50, 95% CI, 0.68 to 3.33 at >60 days).[4] However, opioids evaluated in this study did not include long- or short-acting buprenorphine formulations. A subsequent case control study (n=2,311 cases) was identified in the 2022 update with similar results, but the types of opioids included in the study (i.e., partial vs. full agonists) were not reported.[4,28] Short-term studies of long-acting opioids did not indicate differences in effectiveness or harms with buprenorphine compared to other opioids.[4] Three trials compared transdermal buprenorphine to another long-acting opioid (sustained release tramadol or transdermal fentanyl) with no differences in efficacy (pain, sleep, function, mood) or safety (discontinuation due to adverse events, specific adverse events).[4] No studies were identified which evaluated efficacy and safety of opioid rotation compared to maintenance of current opioid therapy. In patients with pain and comorbid OUD, there was no difference between methadone and buprenorphine/naloxone for outcomes of study retention, pain, function, positive urine drug screen, or illicit drug use (low quality evidence from 2 RCTs).[4]

A 2017 systematic review from CADTH evaluated the evidence for efficacy and safety of buprenorphine for treatment of chronic non-cancer pain.[29] Literature was evaluated from 2011 through 2016. Nine RCTs and 4 systematic reviews (including 18 publications) were included in the evidence review. All the direct comparative evidence evaluated transdermal buprenorphine. Two of the RCTs evaluated buccal buprenorphine. Most evidence was compared to placebo. Active

comparators included tramadol (n=2 studies), morphine (n=1 study), transdermal fentanyl (n=2 studies), codeine (n=1 study), and oxycodone (n=1 study).[29] Most of the identified RCTs had significant risk of bias which limit interpretation of the findings. Seven of the RCTs had high attrition (>30%) or differential drop-out rates between groups.[29] All RCTs except two were manufacturer-funded, and the 2 RCTs without manufacturer funding were open-label studies that were poorly reported and designed.[29] The 4 systematic reviews performed quality assessment of the included trials but it was unclear how they accounted for quality in their conclusions. One network meta-analysis did not provide enough information about their methods to assess the appropriateness of their data analysis. Overall, authors found evidence that buprenorphine resulted in modest pain improvement compared to placebo but no evidence that buprenorphine differed from other opioids.[29] Compared to placebo, the overall benefit of buprenorphine was small and magnitude of benefit failed to achieve clinically meaningful improvements referenced in the literature for several studies.[29] The most common adverse events associated with buprenorphine use were nausea, constipation, vomiting, dizziness, headache, somnolence and application site reactions. There was insufficient evidence to suggest that buprenorphine is associated with fewer harms than other opioids.[29]

A 2014 Cochrane systematic review evaluated opioids for pain associated with osteoarthritis of the hip or knee.[30] The review primarily evaluated oral or transdermal opioids compared to placebo, but results were also stratified based on type of opioid. Twenty-two RCTs were included in the review, and 4 RCTs were identified which evaluated transdermal buprenorphine compared to placebo.[30] Median treatment duration was 4 weeks (range 3 days to 6 months), and median daily dose was 59 daily morphine milligram equivalents (MME; range 13 to 160 MME).[30] Results were generally limited by unclear trial methodology, inadequate reporting of results, small magnitude of benefit, and evidence of publication bias. Opioids were generally associated with a small improvement in pain (standardized mean difference [SMD] -0.31; 95% CI -0.46 to -0.16) and function (SMD -0.26; 95% CI -0.35 to -0.17) compared to placebo.[30] These differences would correspond to an absolute difference of 0.7 cm on a 0 to 10 visual analogue pain scale and a difference of 0.6 points on a standardized Western Ontario and McMaster Universities Arthritis Index (WOMAC) disability scale ranging from 0-10.[30] Results for the buprenorphine subgroup were similar for these outcomes (pain SMD -0.19, 95% CI -0.3 to -0.09 and function SMD -0.23, 95% CI -0.40 to -0.05).[30] Pain improvement was largest in short-term studies and decreased with more than 4 weeks of treatment.[30] Adverse events were more common with opioid treatment than placebo (RR 1.49, 95% CI 1.35 to 1.63 and NNH 14, 95% CI 11 to 19) with no evidence that adverse events differed based on type of opioid.[30] Discontinuations due to adverse events were also more common with opioid treatment (RR 3.76, 95% CI 2.93 to 4.82; NNH 21, 95% CI 15 to 30) and results for the buprenorphine subgroup were similar (RR 3.10, 95% CI 1.38 to 6.94).[30] Most identified trials were industry funded. Overall, authors concluded that opioids provide small benefits for relief of pain and improved function although the magnitude of benefit was of questionable clinical significance. Serious risks associated with long-term use (including discontinuations due to adverse events, addiction, and opioid dependence) likely outweigh any small, long-term benefit.[30]

A Cochrane review published in 2022 evaluated efficacy and safety of opioid agonist treatment in people dependent on pharmaceutical opioids.[11] The review included trials that assessed at least 30 days of maintenance treatment for OUD. Studies with a mixed population of patients who used pharmaceutical opioids or heroin had to have at least 80% of patients with dependence on pharmaceutical opioids.[11] Outcomes of interest for this review included comparisons of partial and full opioid agonists for adverse events, pain, function, and quality of life. Four trials were included which compared methadone to buprenorphine in adults and adolescents with OUD related to pharmaceutical opioids.[11] The mean duration of treatment was 17.4 weeks, and trials primarily included male patients (70%) with a mean age of 32 years.[11] All 4 trials were open-labeled and had unclear allocation concealment. Two of the trials had unclear randomization methods and 3 studies had high or unclear risk for attrition bias. One trial which compared methadone and buprenorphine had high risk of reporting bias and included data on only one outcome (retention in treatment).[11] There was no difference between methadone and buprenorphine for the outcomes of adverse events (RR 1.13; 95% CI 0.66 to 1.93; n=206; low quality evidence).[11] There was also no difference in pain intensity (SMD -0.12, 95% CI -0.73 to 0.50; 3 studies; n=163), physical functioning reported using the 36-item short form (SF-36) scale (MD 1.28; 95% CI -3.83 to 6.39; 1 study; n=127), and none of the studies reported overall quality of life.[11]

An AHRQ systematic review, initially published in 2020 with literature searches updated in 2022, evaluated the efficacy and safety of pharmacologic (opioid and non-opioid) and non-pharmacologic treatments for acute pain.[18] The review did not find any evidence comparing buprenorphine to other opioids for acute back pain, neck pain, peripheral neuropathic pain, post-operative pain, dental pain, or sickle cell crisis.[18] One trial (n=89) compared sublingual buprenorphine 0.4 mg to intravenous morphine 5 mg in patients with an extremity fracture. Mean difference in pain intensity was not different at one hour post-treatment (the average improvement was 2.2 points on 0-10 NRS for both groups).[18] No other efficacy or safety outcomes were reported. A small, fair quality trial (n=26) compared intramuscular buprenorphine 0.3 mg to intramuscular meperidine 100 mg in patients with kidney stone pain. Pain intensity at 12 hours was improved more with buprenorphine compared to meperidine (4.2 vs. 1.2; MD 3.0; 95% CI 2.8 to 3.2) and was associated with less use of rescue medication (92% vs. 46%; RR 2.00, 95% CI 1.09 to 3.67).[18] There was no difference in reported adverse events including nausea and vomiting.[18]

A 2021 systematic review evaluated feasibility, efficacy, and safety of transition to buprenorphine in patients prescribed long-term opioids for chronic pain.[20] Authors used high quality methods to conduct the review including duplicate study identification, data extraction, and quality assessment. Outcomes were prespecified and the quality of evidence was considered in conclusions. However, most studies identified for the review had high risk of bias, lacked a comparison group, and had significant heterogeneity.[20] The review identified 22 studies published through November 2022 including 5 RCTs, 7 case-control or cohort studies, and 10 uncontrolled pre-post studies.[20] Primary outcomes of interest included precipitated opioid withdrawal, pain intensity, pain interference with daily activities, adverse events, and healthcare utilization. Diagnoses of patients included chronic musculoskeletal pain, neuropathic pain, fibromyalgia, and chronic cancer pain. Reasons for transitioning to buprenorphine ranged from escalating opioid doses, aberrant opioid use, adverse effects with current therapy, inadequate analgesia, and drug combinations that increase risk for overdose (e.g., high doses or combination sedative use).[20] In 13 of 22 studies, patients had concomitant OUD, and 4 studies explicitly excluded patients with OUD.[20] Often problematic behavior, aberrant opioid use, or opioid dependence was observed, even in studies that excluded patients with OUD. Previous opioid use also differed among participants with average daily doses of 60-500 MME in the studies. The range of included daily doses was 10 MME to 3,200 MME.[20] The method used to transition to buprenorphine and the buprenorphine dosing regimen also differed between studies. Nine studies required participants to exhibit mild withdrawal symptoms before starting buprenorphine, 8 studies required participants to wait 8-24 hours before initiating buprenorphine, and 3 studies required participants to wait overnight.[20] One study evaluated microdosing of buprenorphine to mitigate withdrawal symptoms and 10 studies allowed use of a variety of other medications to mitigate symptoms.[20] Some studies included a taper for buprenorphine and others established patients on stable doses of buprenorphine maintenance therapy. Sublingual or buccal buprenorphine was used in 13 studies, 2 studies used transdermal buprenorphine, and 2 studies used multiple formulations.[20] Ten studies were conducted in the outpatient or clinic setting and 7 studies were solely in the inpatient setting or started the transition during an inpatient stay before continuing with outpatient treatment.[20] Results were described narratively, and all outcomes were graded as very low quality, indicating a high degree of uncertainty that the study results represent the true treatment effect. Precipitated opioid withdrawal was evaluated in 7 studies and occurred in 3-6% of patients.[20] In most studies, symptoms were mild, but severe withdrawal was observed in some participants (especially those on high opioid doses). Pain intensity was described in 17 studies and was improved in 12 of these studies after transitioning to buprenorphine.[20] Effect size was smaller in studies with control groups and in patients with doses of opioids exceeding 200 MME prior to switching.[20] There was also variability observed based on the study population, the tool used to evaluate pain intensity, and the rationale for switching to buprenorphine.[20] In one study, higher doses of buprenorphine (16 mg daily) were associated with improved pain compared to lower doses (2 mg daily; OR 0.42; 95% CI 0.20-0.90).[20] Only 4 studies evaluated impact of pain on daily functioning after switching with improvement in some individuals but with significant heterogeneity based on population and the tool used to evaluate function. Retention rates (described in 14 studies) ranged from 33 to 93%.[20] Adverse effects (described in 10 studies) were common and similar to other opioids.[20] Severe adverse effects or discontinuation due to adverse effects were less common but long-term follow up was often not systematically evaluated after switching to buprenorphine. No studies evaluated healthcare utilization. The authors concluded that buprenorphine was likely non-inferior to other opioids for pain control based on very low quality evidence.[20] Careful transition to buprenorphine is possible with minimal adverse effects, but the optimal protocol to switch patients to buprenorphine is not known.[20] Only 10 studies reported

following participants for at least 6 months and follow-up periods were not consistent in the observational studies.[20] The significant heterogeneity and small number of patients studied limits the ability to identify important long-term outcomes such as overdose, mortality, and development of opioid use disorder.

A 2017 Cochrane review evaluated adverse events associated with medium and long-term use of opioids for chronic non-cancer pain.[31] The review included 61 studies (n=18,679 patients).[31] Trials were included if they evaluated opioid use of 2 weeks or more, and most studies evaluated opioids over 6 to 16 weeks. Outcomes evaluated included any adverse event, serious adverse events and withdrawals due to adverse events. Differences between opioids was not evaluated. However, compared to placebo, opioid therapy was associated with an increased risk of any adverse event (78% vs. 54%; RR 1.42, 95% CI 1.22 to 1.66), withdrawals due to adverse events (25.1% vs. 7.1%; RR 3.40, 95% CI 3.02 to 3.82), and serious adverse events (7.5% vs. 4.0%; RR 2.75, 95% CI 2.06 to 3.67) based on moderate quality evidence.[31] Several other specific adverse events were also more common with opioid treatment than placebo including constipation, dizziness, drowsiness or somnolence, nausea, sweating based on moderate quality evidence.[31] There was very low quality evidence that pruritus, vomiting, hot flushes, and fatigue were more common with opioid treatment compared to placebo.[31]

Systematic reviews have evaluated opioids for acute pancreatitis pain (2013),[32] chronic non-cancer pain in children and adolescents (2017),[33] chronic neuropathic pain (2015),[34] acute pain in the pre-hospital setting,[35] and high-dose opioids (>200 daily MME) in chronic non-cancer pain.[36] Overall, these reviews did not identify trials that evaluated sublingual, buccal or transdermal buprenorphine for treatment of pain. Other systematic reviews did not identify any direct comparative data for buprenorphine in chronic low back pain (2013).[37]

After review, 30 systematic reviews were excluded due to poor quality (e.g., network meta-analyses, inadequate reporting of methods), comparator (e.g., non-opioid or placebo-controlled), wrong population (e.g., cancer pain, substance use disorder), or outcome studied (e.g., non-clinical).

Guidelines:
CDC guidelines were updated in 2022 and addressed the use of opioids for treatment of acute pain (less than 1 month), subacute pain (1 to 3 months), and chronic pain (more than 3 months) pain.[6] The guideline excluded cancer-related pain, pain related to sickle cell disease or palliative care. Recommendations were based primarily on 5 systematic reviews from AHRQ on treatments for opioids, non-opioids, and nonpharmacologic treatments for chronic pain, treatment for episodic migraine, and treatment for acute non-migraine pain.[6] Evidence from these reviews was supplemented by a contextual evidence review of resource allocation and patient and provider values and preferences. Recommendations were graded according to evidence type (**Table 3**) and grouped into category A or B recommendations. Most recommendations were made based on type 4 (low quality) evidence.[6] Recommendation categories were determined based primarily on 4 factors: the quality of the evidence, balance between desirable and undesirable outcomes, values and preferences, and resource allocation (e.g., costs to patients or health systems).[6] Category A recommendations are more likely to apply to all people in the group and category B recommendations indicate that the recommendation might not apply to all people and clinicians should employ shared decision-making to find the most appropriate decision for the specific clinical situation. The guideline was intended to serve as a clinical tool to improve patient-centered decisions related to pain management and was not intended to serve as inflexible standards of care.[6]

Table 3. CDC Categorization for Evidence Types and Recommendations

Evidence Type	Description	Approximate AHRQ strength of evidence equivalent
Type 1	randomized clinical trials or overwhelming evidence from observational studies	High
Type 2	randomized clinical trials with important limitations, or exceptionally strong evidence from observational studies	Moderate

Type 3	observational studies, or randomized clinical trials with notable limitations	Low
Type 4	clinical experience and observations, observational studies with important limitations, or randomized clinical trials with several major limitations	Low with serious limitations

Opioids generally provided a small improvement in pain and function compared to placebo, but were also associated with short-term harms with evidence of pain attenuation with longer-term use between 3-6 months.[6] Twelve recommendations highlighted in **Table 4** were included to guide the use of opioids.[6] Specific recommendations for initiation and choice in therapy are outlined below, and additional recommendations for monitoring are included in **Table 4**.

- Clinicians should maximize the use of non-opioid therapies (including any non-pharmacological therapies appropriate for the condition) before prescribing opioids for acute, subacute, and chronic pain. No difference in pain or function was found between opioids and NSAIDs for multiple chronic conditions.[6]
- Before starting opioid therapy for subacute or chronic pain, clinicians should discuss with patients the realistic benefits and known risks of opioid therapy, should work with patients to establish treatment goals for pain and function, and should consider how opioid therapy will be discontinued if benefits do not outweigh risks.
- Clinicians should use caution when prescribing opioid pain medication and benzodiazepines concurrently and consider whether benefits outweigh risks of concurrent prescribing of opioids and other central nervous system depressants. Concomitant use has been associated with increased risk of overdose and death in observational studies.
- When starting opioid therapy, prescribe short-acting opioid formulations instead of long-acting opioid formulations. Evidence demonstrates treatment response of pain and function is generally consistent across duration of action of the opioid product (short or long-acting) and opioid type (full agonists, partial agonists, or mixed mechanisms) for chronic pain.[6] Time-scheduled use of extended-release opioids was not more effective or safe than intermittent use of short-acting opioids and has been associated with greater total average daily doses than short-acting formulations.[6] With regard to harms, a fair quality observational study found a higher risk of overdose with long-acting opioids versus immediate-release opioids.[6] No distinction was made between extended-release buprenorphine and other extended-release opioid formulations. Risk was highest with initial treatment and decreased with longer exposure.[6] The FDA recommends long-acting opioid formulations for pain severe enough to require daily, around-the-clock treatment, and when other treatment options, including non-opioids and short-acting opioids, are ineffective, intolerable, or provide inadequate pain relief.[6] Long-acting opioids should not be used on an as-needed basis.
- Prescribe the lowest dose and shortest duration indicated based on patient specific risk factors. Data from observational studies show short-term opioid use is associated with progression to long-term opioid use and long-term opioid use is associated with increased risk for serious harms (including opioid use disorder and overdose).[6] Harms related to opioid use increases with higher opioid doses, without a minimum dose below which there is no risk.
- For patients already receiving opioid therapy, clinicians should carefully weigh benefits and risks and exercise care when changing opioid dosage. In patients established on long-term opioid therapy, tapering or discontinuing opioids can be difficult and be associated with significant harms. A collaborative, patient-centered approach to opioid tapering is recommended. If patients remain on opioid treatment, incorporation of risk mitigation strategies should be considered.
- No specific recommendations were made for buprenorphine, though guideline authors note that it may have utility for patients on high-dose opioids when risks outweigh benefits but who are unable to taper and who do not meet criteria for opioid use disorder.[6] Based on limited, emerging evidence, transitioning to buprenorphine may be one strategy to assist patients with decreasing total opioid dose. However, caution is advised when transitioning between full opioid agonists and buprenorphine. The current standard method to transition to buprenorphine from a full agonist is to wait until the patient exhibits mild to moderate withdrawal symptoms before starting buprenorphine, then to titrate buprenorphine under supervision every 2 hours

to control withdrawal symptoms.[6] Protocols to transition patients vary significantly, but have been described in both the inpatient and outpatient settings.[6] Several case series have also described a low-dose initiation approach (i.e., microdosing) of buprenorphine to avoid and mitigate withdrawal symptoms during transition, but evidence for this new approach is limited.[6] Guideline authors note that the comparative efficacy and harms of buprenorphine compared to full opioid agonists is an important area for future research.[6]

Table 4. CDC Recommendations for Prescribing Opioids for Pain[6]

	Recommendation	Evidence Type	Category
Determining Whether or Not to Initiate Opioids for Pain			
1	Nonopioid therapies are at least as effective as opioids for many common types of acute pain. Clinicians should maximize use of nonpharmacologic and nonopioid pharmacologic therapies as appropriate for the specific condition and patient and only consider opioid therapy for acute pain if benefits are anticipated to outweigh risks to the patient. Before prescribing opioid therapy for acute pain, clinicians should discuss with patients the realistic benefits and known risks of opioid therapy.	3	B
2	Nonopioid therapies are preferred for subacute and chronic pain. Clinicians should maximize use of nonpharmacologic and nonopioid pharmacologic therapies as appropriate for the specific condition and patient and only consider initiating opioid therapy if expected benefits for pain and function are anticipated to outweigh risks to the patient. Before starting opioid therapy for subacute or chronic pain, clinicians should discuss with patients the realistic benefits and known risks of opioid therapy, should work with patients to establish treatment goals for pain and function, and should consider how opioid therapy will be discontinued if benefits do not outweigh risks.	2	A
Selecting Opioids and Determining Opioid Dosages			
3	When starting opioid therapy for acute, subacute, or chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release and long-acting (ER/LA) opioids.	4	A
4	When opioids are initiated for opioid-naïve patients with acute, subacute, or chronic pain, clinicians should prescribe the lowest effective dosage. If opioids are continued for subacute or chronic pain, clinicians should use caution when prescribing opioids at any dosage, should carefully evaluate individual benefits and risks when considering increasing dosage, and should avoid increasing dosage above levels likely to yield diminishing returns in benefits relative to risks to patients.	3	A
5	For patients already receiving opioid therapy, clinicians should carefully weigh benefits and risks and exercise care when changing opioid dosage. If benefits outweigh risks of continued opioid therapy, clinicians should work closely with patients to optimize nonopioid therapies while continuing opioid therapy. If benefits do not outweigh risks of continued opioid therapy, clinicians should optimize other therapies and work closely with patients to gradually taper to lower dosages or, if warranted based on the individual circumstances of the patient, appropriately taper and discontinue opioids. Unless there are indications of a life-threatening issue such as warning signs of impending overdose (e.g., confusion, sedation, or slurred speech), opioid therapy should not be discontinued abruptly, and clinicians should not rapidly reduce opioid dosages from higher dosages.	4	B
Deciding Duration of Initial Opioid Prescription and Conducting Follow-up			
6	When opioids are needed for acute pain, clinicians should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids.	4	A

7	Clinicians should evaluate benefits and risks with patients within 1–4 weeks of starting opioid therapy for subacute or chronic pain or of dosage escalation. Clinicians should regularly reevaluate benefits and risks of continued opioid therapy with patients.	4	A
Assessing Risks and Addressing Potential Harms of Opioids			
8	Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk for opioid-related harms and discuss risk with patients. Clinicians should work with patients to incorporate into the management plan strategies to mitigate risk, including offering naloxone.	4	A
9	When prescribing initial opioid therapy for acute, subacute, or chronic pain, and periodically during opioid therapy for chronic pain, clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or combinations that put the patient at high risk for overdose.	4	B
10	When prescribing opioids for subacute or chronic pain, clinicians should consider the benefits and risks of toxicology testing to assess for prescribed medications as well as other prescribed and nonprescribed controlled substances.	4	B
11	Clinicians should use caution when prescribing opioid pain medication and benzodiazepines concurrently and consider whether benefits outweigh risks of concurrent prescribing of opioids and other central nervous system depressants.	3	B
12	Clinicians should offer or arrange treatment with evidence-based medications to treat patients with opioid use disorder. Detoxification on its own, without medications for opioid use disorder, is not recommended for opioid use disorder because of increased risks for resuming drug use, overdose, and overdose death.	1	A

Chronic Pain

Guidelines from the U.S. Department of Defense and Veterans Affairs were updated in May 2022 for the management of opioids in patients with chronic pain.[1] Management of acute pain was not addressed in this guideline. General recommendations for use and monitoring of opioids for chronic pain were consistent with the CDC guideline recommendations outlined above. Careful evaluation of risks and benefits of long-term opioid therapy is particularly recommended in younger patients or patients with co-occurring substance use disorders as these populations may have increased risk of adverse events.[1]

The guideline evaluated evidence for, and use of, specific types of opioids in several circumstances.

- Prescription of long-acting opioids was *strongly recommended against* for acute pain, on an as-needed basis, or when planned long-term opioid therapy is initiated.[1] Authors did not differentiate between long-acting buprenorphine buccal or transdermal formulations and other long-acting opioid formulations. This recommendation was based on moderate quality evidence from a large retrospective cohort study which found an increased risk of treatment for OUD when patients were prescribed long-acting opioids compared to short-acting opioids.[1] A second study identified that patients prescribed long-acting opioids and schedule II opioids had a 4.7-times increased risk to die from an overdose than patients prescribed non-schedule II opioids based on low quality evidence.[1]
- For patients on daily, moderate to high dose, long-term opioids for chronic pain, use of buprenorphine is *weakly recommended* instead of full agonist opioids.[1] Overall, there was insufficient evidence that compared buprenorphine to other opioids.[1] The authors felt, however, that the theoretical safety profile of buprenorphine based on the mechanism of action as a partial agonist and status as a schedule III substance may potentially decrease long-term risks compared to full opioid agonists which are classified as schedule II substances and have well known overdose risks.[1]
    - Evidence for this recommendation included three systematic reviews in patients with chronic pain, neuopathic pain, and low back pain evaluated opioids compared to placebo or non-opioid analgesics. There were no direct comparative data evaluating buccal and transdermal buprenorphine versus other opioids, and outcomes were generally not reported for specific opioids. Indirect comparative data from 2 network

meta-analyses evaluated opioids for chronic pain and chronic low back pain. In patients with chronic low back pain, buprenorphine did not differ from hydrocodone, hydromorphone, morphine, oxycodone, oxymorphone, tramadol, and tapentadol for most efficacy outcomes.[1] There was low quality evidence that buprenorphine may achieve 30% pain reduction more than tramadol, but several study biases like lack of reporting on duration of chronic pain and prior treatments of opioids limit this evidence.[1] Because of the narrow inclusion criteria for trials in this analysis, applicability to other populations and other chronic pain conditions is also unclear. The second network meta-analyses evaluated safety of tapentadol to other opioids. Serious adverse events and discontinuation due to adverse events did not differ between tapentadol and buprenorphine.[1] Compared to tapentadol, buprenorphine may be associated with a lower rate of any adverse event based on low quality evidence.[1] This difference in any adverse event was primarily driven by differences in constipation with tapentadol compared to buprenorphine.[1]
    - The authors noted that this recommendation for buprenorphine should be weighed against the paucity of evidence, especially in patients who are opioid-naïve, patients who are opioid-experienced with low or intermittent dosing, and patients who concomitantly use other central nervous system depressants.[1] Most studies reported a maximum follow-up of 1 to 6 months, trials commonly lacked adequate description of methods to control for bias, and most studies were funded by industry.[1] RCTs also often excluded patients at highest risk for poor outcomes. For example, patients with behavioral health comorbidities, including substance use disorders, were excluded. Long-term observational trials have also shown a higher opioid dose and longer duration of prescribed opioids leads to increased risk of treatment for OUD and fatal overdoses.[1] The authors concluded that any potential benefit of short-term opioid therapy is likely outweighed by these serious adverse events, even in carefully selected patients.[1]
- For management of chronic pain in the setting of co-occurring OUD, there was insufficient evidence to compare methadone, buprenorphine, or extended-release naltrexone injection and make a recommendation for one drug therapy over another.[1] The authors recommend OUD be treated in accordance with current guidelines.
    - A systematic literature search identified a single RCT (n=159) that compared extended-release naltrexone and buprenorphine/naloxone for treatment of chronic pain in the setting of OUD over 12 weeks. Pain intensity did not significantly worsen in either treatment group over 12 weeks, but evidence was limited by low study retention, imprecision, risk of bias, and applicability issues as patients with severe chronic pain were not encouraged to participate.[1]
    - Supporting evidence also included a systematic review (14 studies, n=3128) which evaluated the impact chronic pain had on outcomes in patients with OUD. Evidence was limited by inconsistency across outcome definitions and risk of bias. Chronic pain was associated with comorbid psychiatric conditions (OR 2.18; 95% CI 1.6 to 2.9), but did not impact any outcomes for patients on buprenorphine or buprenorphine/naloxone.[1]
    - Based on this evidence, it was concluded that the presence of chronic pain is not a reason to withhold MAT in patients with comorbid OUD.[1]

Guidelines updated in May 2021 from the Department of Defense/Veterans Administration for the management of patients with chronic multisystem illness (CMI) also included recommendation for opioids for treatment of chronic pain.[38] CMI was defined as presence of multiple symptoms (e.g., fatigue, headache, myalgias, arthralgias, concentration problems, gastrointestinal disorders) associated with more than one body system which persist for more than 6 months and interfere with daily functioning. CMI is typically considered when other health conditions have been ruled out. The presence of other conditions like fibromyalgia, irritable bowel syndrome, or chronic fatigue, however, does not preclude diagnosis of CMI. Patients with CMI often have multiple comorbidities. These guidelines *strongly recommend against* the long-term use of opioids for the management of chronic pain in patients with CMI.[38] A systematic review did not identify any studies which evaluated the short- or long-term efficacy of opioids in patients with CMI. Harms and burden of long-term opioid therapy, including risk of overdose and development of OUD, have been associated with opioid prescribing. There is also a lack of high quality evidence which shows that

long-term opioid therapy improves pain, function, or quality of life. Given the lack of evidence, recommendations were made to avoid initiation of opioids for chronic pain in patients with CMI and to prescribe naloxone to mitigate risk in patients who are already established on chronic opioid therapy.[38]

NICE guidelines for the management of chronic pain in adults over 16 years of age were updated in 2021.[3] Recommendations were applicable to chronic primary and secondary pain. Chronic primary pain was defined as pain that persists or recurs for more than 3 months in the absence of a clear underlying condition or cause such as fibromyalgia. Chronic secondary pain pertains to pain related to or caused by an underlying condition. NICE recommendations were based on an evidence review which evaluated treatments for chronic pain and included recommendations for both non-pharmacological and pharmacological treatments. No evidence was identified which evaluated efficacy of the following interventions for chronic pain (defined as >3 months): opioids, acetaminophen, steroids, anesthetics/steroid combination, ketamine and anti-psychotics. One common reason studies of opioids were excluded from the review was because they studied pain caused by other conditions like cancer, neuropathic pain, and musculoskeletal disease, instead of chronic primary pain.[3] No studies identified evaluated the safety of opioids versus placebo, no treatment, or usual care for longer than 6 months. Three observational studies with high risk of bias were included to assess harms of chronic opioid use. Two of the studied assessed opioid use in Medicaid populations and one assessed opioid use in U.S. veterans. Risk of opioid abuse or misuse in these 3 studies ranged from 1.3% to 5.9%.[3] All-cause mortality with opioid use greater than 180 days was 1.1%.[3] No evidence was identified for cognitive impairment, fractures and falls, sexual dysfunction, endocrine impairment, immune dysfunction, sleep apnea, cardiovascular events, self-harm, suicide, or depressive symptoms or mood disturbances in relation to opioids.[3]

Recommendations for pharmacological management included the following:[3]

- Consider an antidepressant like amitriptyline, citalopram, duloxetine, fluoxetine, paroxetine or sertraline in adults with chronic primary pain after discussion of risks and benefits. A consultation with a specialist is recommended for use of antidepressants to manage chronic pain in adolescents less than 18 years of age.
- Do not initiate any of the following medications for chronic primary pain: opioids, acetaminophen, NSAIDs, antiepileptic drugs including gabapentinoids, antipsychotics, benzodiazepines, corticosteroid or local anesthetic/corticosteroid trigger point injections, ketamine, or local anesthetics (topical or intravenous).
- For patients already prescribed non-recommended therapy for chronic pain, recommendations were consistent with CDC and Veterans Administration guidelines for chronic pain including re-evaluation of therapy and shared decision-making to reduce, discontinue, or safely continue the medication.

Guidelines from the Scottish Intercollegiate Guidelines Network for treatment of chronic pain were updated in 2019.[5] No recommendations were made for one opioid over another. Instead, opioid therapy is recommended only for short- to medium-term duration in carefully selected patients with chronic non-malignant pain if other therapies have been insufficient and benefits outweigh risks of serious harms such as addiction, overdose and death.[5] At initiation of therapy, expected outcomes should be established; if not attained, it is recommended that the provider and patient a planned agreement in advance to reduce and stop opioids. Assessment of effectiveness and harms, including signs of abuse and addiction, should occur early after initiation and be reassessed annually, or more frequently if needed.[5] Screening tools to evaluate patients at risk for OUD may be useful as part of a more comprehensive reassessment, but should not be the only tool used. Patients on greater than 50 MME daily should be reviewed more frequently to detect emerging harms. Patients prescribed more than 90 MME should be referred to a pain specialist.[5]

Osteoarthritis

Guidelines from the Department of Defense and Veterans Affairs for the management of osteoarthritis were updated in 2020.[39] Therapies with strong recommendations included use of topical NSAIDs for pain associated with osteoarthritis of the knee.[39] There was insufficient evidence for topical NSAIDs or capsaicin in treatment of osteoarthritis of the hip.[39] There were weak recommendations for topical capsaicin for osteoarthritis of the knee and weak recommendations for acetaminophen or oral NSAIDs for osteoarthritis of the hip and knee. Adjunctive duloxetine also had weak recommendations for osteoarthritis of the knee if there is an inadequate response or contraindications to acetaminophen or NSAIDs.[39] The following recommendations were made for use of opioids:

- The guideline recommend against initiating opioids, including tramadol, for pain associated with osteoarthritis of the hip and knee (weak recommendation against treatment; very low quality of evidence).[39] Other recommendations were consistent the current VA/DoD Clinical Practice Guideline for the Management of Opioid Therapy for Chronic Pain. Non-pharmacological treatment is recommended for pain associated with osteoarthritis; when pharmacological treatment is deemed necessary, non-opioids are recommended over opioids.[39] In patients with persistent pain despite alternative non-opioid or non-pharmacologic treatments, patients should be carefully evaluated to determine if potential benefits of opioid therapy outweigh risks. If opioid therapy is needed, the shortest duration and the lowest effective dose should be used with routine monitoring.[39]
- Opioid recommendations were made based on systematic reviews and RCTs which compared opioids to placebo or active control.[39] No studies were identified in the systematic review that included buprenorphine. Overall, opioids consistently reduced pain intensity more than placebo for hip and knee osteoarthritis, but effect sizes were small and did not often achieve clinically significant differences.[39] Physical functioning was also improved with opioids, but effect was small.[39] Opioids had a higher risk of harms than placebo, including withdrawal due to adverse events, withdrawal symptoms from opioids, and serious adverse events.[39] Trials that compared opioids to non-opioid analgesics like NSAIDs and acetaminophen showed similar, or improved efficacy, with the non-opioid analgesic for function and pain reduction.[39] The trials had short durations of 1-17 weeks.[39]

Guidelines from NICE for management of osteoarthritis were updated in 2022.[40] Recommendations for pharmacologic treatment were consistent with 2020 guidelines from the Department of Defense and Veterans Affairs. Pharmacologic therapies are recommended only in conjunction with non-pharmacologic therapies and to support therapeutic exercise.

- Topical NSAIDs are recommended for osteoarthritis of the knee and may be considered for osteoarthritris associated with other joints.[40] If topical NSAIDs are ineffective, an oral NSAID can be considered based on individual risks for gastrointestinal, renal, liver, cardiovascular, and pregnancy-related adverse events.[40]
- Codeine and acetaminophen are recommended only for infrequent, short-term pain relief, and only when other pharmacological treatments are contraindicated, intolerable, or ineffective.[40]
- Opioids, excluding codeine, are not recommended because risks outweigh benefits for patients with osteoarthritis.[40]

Evidence for these recommendations included only a few studies that evaluated buprenorphine for osteoarthritis. One trial compared transdermal buprenorphine to oral tramadol and 2 studies that compared transdermal buprenorphine to placebo.[40] No difference in pain was found between buprenorphine and tramadol based on low quality evidence (NRS 0-10 scale: MD 0.18 lower; 95% CI 0.9 lower to 0.54 higher); in addition, no difference in serious cardiovascular events was found at 12 weeks based on very low quality evidence (60 more per 1,000; 95% CI 0 fewer to 120 more).[40] There was insufficient evidence for all other efficacy and safety outcomes. The guideline noted that trials of transdermal opioids have generally failed to include patients over 75 years of age, and there are little data to guide choice of therapy with regard to route of administration for this patient population.[40]

Low Back Pain

Guidelines were updated in February 2022 from the Department of Defense and Veterans Affairs for the management of patients with low back pain.[41] There were no non-pharmacologic or pharmacologic treatments which had a strong recommendation for treatment. Pharmacotherapy recommended for management of low back pain included duloxetine and NSAIDs (weak recommendation for treatment).[41] There was insufficient evidence to recommend gabapentin, pregabalin, tricyclic antidepressants, topical analgesics, or short-term use of muscle relaxants for low back pain.[41] Recommendations were made against the use of opioids, acetaminophen, investigational monoclonal antibodies, systemic corticosteroids, and chronic use of muscle relaxants (weak recommendation against treatment).[41] There was a strong recommendation against the use of benzodiazepines for low back pain.[41] Recommendations against use of opioids were primarily made based on the following evidence:

- A systemic review and meta-analysis of 21 RCTs in patients with chronic low back pain.[42] Trials were included if they were at least 4 weeks duration. Four of the trials evaluated transdermal or buccal buprenorphine against placebo. No head-to-head comparative evidence between opioids were identified except one study that compared tapentadol with oxycodone.[42] Subgroup analyses did not include buprenorphine compared to other opioids. Compared to placebo, opioids had a greater reduction in disability based on moderate quality evidence and improved pain severity based on moderate to low quality evidence for various pain measures at 4 to 15 weeks.[42] No differences in serious adverse events or mortality with short-term use were found based on low quality evidence. Subgroup analyses indicate that discontinuation of opioids was more common with longer-term studies greater than 12 weeks' duration. There was insufficient evidence to evaluate efficacy and safety of long-term opioid therapy greater than 6 months.[42] Study limitations included lack of assessment of abuse and addiction. Most studies excluded patients who may be at higher risk for overdose or dependence. Patients with comorbid somatic or psychiatric diseases and current or previous substance use were excluded.[42] Applicability to Medicaid populations was further limited as none of the studies were conducted in the primary care setting. Trials also lacked patient diversity as most enrolled participants were middle-aged White women.[42] It is unclear how inclusion of a broader population of patients, particularly patients with comorbidities, or different healthcare settings like primary care, into clinical trials could impact existing evidence.
- Two systematic reviews that evaluated the efficacy and safety of opioids in chronic and acute low back pain.[14,43] These reviews were also included in the 2017 VA/DOD guideline for chronic pain. The reviews showed modest improvement with opioids compared to placebo for pain intensity in patients with acute or chronic low back pain (MD of -8.1 on a 0-100 visual analogue scale and MD -0.43 on a 0-10 numeric rating scale). The proportion of patients who achieved a clinically important improvement in pain intensity of 30% or greater was not reported. In a meta-analysis of 3 RCTs, function was not clinically improved over 30-91 days with opioid therapy compared to placebo, but results were limited by wide confidence intervals.[14] The other meta-analysis demonstrated a small, clinically unimportant difference in function compared to placebo (SMD of -0.26, or about 1 point on a 24 point Roland-Morris Disability Questionnaire).[43] There was insufficient direct comparative evidence from both of these systematic review to evaluate different opioids for outcomes of pain or function. Two trials compared transdermal buprenorphine to placebo and provide low quality evidence for a small improvement in pain (<1 point on a 10-point scale) which is like other opioids. There is insufficient evidence with transdermal buprenorphine to determine differences in function compared to placebo in patients with chronic low pain.[43] Adverse events were more common with opioids than placebo (68.9% vs. 49.1%, respectively). In 4 trials, more than 50% of patients discontinued opioid treatment due to adverse events or lack of efficacy.[14,41]

Overall, guideline authors concluded that the small potential benefit with short-term opioid use over 4-15 weeks may be substantially outweighed by the potential serious harms of opioids including potentially fatal respiratory depression, overdose, misuse, abuse, addiction, and diversion.[41]

Guidelines from NICE for the management of low back pain and sciatica were published in 2016 and last updated in 2020.[44] Recommendations were made against use for opioids, gabapentinoids, other antiepileptics, oral corticosteroids, and benzodiazepines due to lack of evidence for benefit and evidence of harm associated with these treatments.[44] A systematic review of treatments for sciatica and low back pain failed to identify evidence for use of opioids compared to

placebo, usual care, or other treatments.[44] Studies of patients with mixed chronic pain were excluded. In the absence of specific evidence, the following recommendations for opioids were made based on clinical experience of the guideline committee:[44]

- Do not offer opioids for management of *chronic* sciatica or *chronic* low back pain because risks of long-term use likely outweigh benefits.
- Do not routinely offer opioids for managing *acute* low back pain.
- Codeine with or without acetaminophen may be considered for acute low back pain if an NSAID is contraindicated, intolerable or ineffective.
- For patients already established on opioid therapy, a discussion of risks, including risk of withdrawal, are recommended. A plan with shared decision making on whether to discontinue these agents should be formulated.

Other guidelines which briefly mention the use of opioids include:

- NICE guidelines updated in 2018 for the management of acute pyelonephritis.[45] Low doses of codeine can be considered for acute pain management in patients over 12 years of age if pain is not controlled with acetaminophen alone. No recommendations were made for other opioids or for long-term use of opioids.[45]
- NICE guidelines for the treatment of neuropathic pain were published in 2013 and last updated in 2020.[2] Recommendations for initial choice of treatment include amitriptyline, duloxetine, gabapentin, or pregabalin.[2] If initial treatment is ineffective or not tolerated, switching therapy to another one of these agents is recommended.[2] Tramadol is only recommended if acute rescue therapy is needed.[2] There are recommendations against long-term use of tramadol for neuropathic pain. NICE recommends against use of other opioids unless recommended by a specialist.[2] Referral to a specialist is recommended upon initial assessment if patients have severe pain, if pain significantly impacts quality of life or function, or if their underlying health condition has deteriorated.[2]

<u>Additional Guidelines for Clinical Context:</u>

In response to increasing post-marketing reports of harms associated with abrupt discontinuation or rapid dose reduction with opioids, the US department of Health and Human Services (HHS) published guidance in October 2019 for clinicians on appropriate dose reduction and discontinuation of long-term opioids.[46] Methods used to develop this guideline were not reported, though at least some recommendations were adapted from the Oregon Pain Guidance Workgroups.[46] Recommendations in this guideline were not graded, and the quality of the recommendations could not be assessed.[46] These guidelines emphasize the importance of care coordination and individualized patient care during initiation of an opioid taper plan in order to avoid risks associated with rapid discontinuation. Risks of abrupt or rapid tapers can include withdrawal symptoms, worsening pain, psychological stress, suicidality, seeking opioids from high-risk sources, and loss of patient trust.[46] Required tapering should be avoided, particularly when benefits of opioid therapy continue to outweigh risks. Instead, the decision to taper opioids should be based on a shared decision between the patient and provider.[46] Use of shared decision making when developing tapers helps to establish trust with the patient, ensures patient-focused tapering, incorporates the patient's values into the taper plan, provides education on the risks of opioid use, and establishes realistic goals and expectations.[46] The HHS guidelines recommend tapering to a reduced dose or discontinuation of opioid therapy be considered in the following circumstances:[46]

- When pain improves
- When pain and function are not meaningfully improved
- Upon receipt of higher doses without documented benefit from higher dose
- When there is evidence of opioid misuse
- With significant adverse effects which affect quality of life or function
- When the patient experiences an overdose or with warning signs for overdose of confusion, sedation or slurred speech

- With co-prescribing of sedating medications or comorbid conditions that increase risk for adverse events
- With long-term prescribing and current risk-benefit assessment is unclear

Various tools and methods recommended to support dosage reduction include individualized dose reductions based on patient history and goals and supportive therapy using a multidisciplinary treatment approach to improve outcomes.[46] Guidelines emphasize flexible taper plans, integration of non-pharmacologic and non-opioid pharmacologic treatments into the treatment plan, use of behavioral health supports, and addition of appropriate symptomatic treatment as needed.[46] They also suggest transitioning to buprenorphine for patients who are unsuccessful with slow tapers when risks of opioid therapy outweigh benefits.[46]

After review, one guideline was excluded due to poor quality.[47]

Dependence and Abuse Potential:
Buprenorphine is currently categorized as a schedule III substance by the Drug Enforcement Agency (DEA), whereas many other long-acting opioids are categorized as schedule II substances. Data on abuse potential of buprenorphine were primarily derived from short-term studies with few participants in controlled clinical settings.[48-53] There are few small pharmacokinetic studies conducted in controlled clinical settings which evaluate risk of overdose and respiratory depression with buprenorphine compared to other opioids,[54,55] but it is unknown if these results could be generalized to the real world. Large observational cohort studies have documented increased risk of death and overdose with long-acting opioid formulations. This risk is thought to be due to increased opioid exposure associated with scheduled, around-the-clock, long-acting formulations versus short-acting opioids, which may be used more frequently on an as-needed basis.[28,56,57] Long-acting formulations of buprenorphine were not included in these studies.

The utility of naloxone for reversal of respiratory depression caused by buprenorphine has also been evaluated in controlled clinical settings with healthy participants, but the applicability of these results to a larger population in the outpatient setting is unclear.[54] FDA labeling for transdermal and buccal buprenorphine notes that rescue doses of naloxone may not be effective for reversal of respiratory depression associated with buprenorphine, and higher doses of naloxone may not provide higher odds of reverasal.[9,10] The effects of naloxone may be delayed by 30 minutes or more.[9,10]

In a 2020 report from the National Poison Data System, buprenorphine was identified in a total of 4,958 exposure cases, of which 2,948 cases were single exposures involving only buprenorphine.[58] Thirty-eight percent of single exposures (n=1,143) were in children less than or equal to 5 years of age and almost 50% (n=1,450) were in adults at least 20 years of age.[58] The exposure was classified as unintentional in 56% of cases (n=1,667) and intentional in 30% of exposures (n=883).[58] Over 70% of cases (n=2,107) received treatment in a healthcare facility. The proportion of patients who received naloxone after exposure was not reported. Medical outcomes for these exposures were classified according to symptom severity. Forty percent of cases (n=1,172) were classified as having no symptoms or only mild symptoms, defined as typically not needing an intervention. Moderate or major outcomes occurred in 623 (21%) and 125 (4%) cases, respectively.[58] Moderate outcomes were classified as symptoms severe enough to warrant treatment and major outcomes are typically classified as life-threatening or resulted in significant residual disability or disfigurement (e.g., repeated seizures or status epilepticus, respiratory compromise requiring intubation, ventricular tachycardia with hypotension, cardiac or respiratory arrest, esophageal stricture, and disseminated intravascular coagulation).[58] Two fatalities were identified from single exposure to buprenorphine.[58] Cases involving a single substance generally reflect most exposures, identified at 87.7% from these data, but are responsible for only 44.7% of fatalities.[58]

Randomized Controlled Trials:

A total of 328 citations were manually reviewed from the initial literature search. After further review, all studies except 4 RCTs were excluded because of wrong study design (e.g., observational), comparator (e.g., no control, non-opioid control, or placebo-controlled), outcome studied (e.g., non-clinical), or inclusion in the systematic reviews described above. The remaining 4 trials are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 5. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Londhe, et al. 2020.[59] Single site, RCT N=200	1. Transdermal buprenorphine 5 mcg/h applied after surgery for 15 days 2. IV APAP 1 gm and tramadol 50 mg every 8 h for 2 days before switching to oral treatment Duration: 7 days	Patients with total knee arthroplasty India	Pain intensity assessed using 0-100 visual analogue scale for up to 7 days post-surgery	Day 1 post-surgery 1. 30 2. 40 Day 7 post-surgery 1. 10 2. 30 P=0.0083 over 7 days	High risk for selection bias: Method to allocate patients to groups was even/odd allocation which is not random. High risk for performance and detection bias: Blinding of patients, providers, and outcome assessors was not reported. Attrition was not documented.
Lee, et al. 2017.[60] OL, MC, NI, RCT N=136	1. Transdermal buprenorphine 5-20 mcg/h weekly 2. Tramadol/APAP 37.5/325mg tablets given twice daily (titrated up to 4 tablets twice daily as needed) Dose was titrated based on pain intensity Duration: 6 weeks	Adults with persistent postoperative pain (NRS ≥4) at 14-90 days after lumbar fusion surgery South Korea	Improvement in pain intensity at 6 weeks on the NRS scale (non-inferiority margin of 1.5)	Pain improvement from baseline to 6 weeks 1. 2.02 ± 2.14 2. 2.76 ± 1.45 MD 0.74; lower 97% CI was -1.45 indicating buprenorphine was not non-inferior to tramadol/APAP	High risk for performance and detection bias due to open label design. High risk for attrition bias (36% did not complete the study).
Kim, et al. 2017.[61] Single-center, OL, NI, RCT N=71	1. Transdermal buprenorphine 5 mcg/h patch 2. Oral tramadol 150-300 mg daily Patients were randomized at 36 h post-surgery and patient-controlled analgesia was discontinued at 72 h post-surgery Duration: 4 weeks	Adults with single level posterior lumbar interbody fusion surgery South Korea	Pain intensity for lower back pain at 7 days post surgery (measured by 1-10 visual analogue scale; non-inferiority margin of 1.5)	Pain intensity at 7 days 1. 3.59 ± 1.62 2. 3.50 ± 1.61 MD 0.09 (95% CI -0.75 to 0.94) Pain severity with buprenorphine was non-inferior to tramadol at 7 days	Unclear risk of selection bias as randomization method was not specified. High risk for performance and detection bias due to open label design. High risk for attrition bias (11 and 18% of patients had missing outcome data at 7 days in tramadol and buprenorphine groups, respectively).

Desai, et al. 2017.[62] Single-center, OL, RCT N=50	1. Transdermal buprenorphine 10 mcg/h patch applied the day before surgery 2. Tramadol 50 mg pre-operatively and three times daily post-operatively Duration: 7 days	Adults undergoing surgery for proximal femur fractures India	Pain intensity at up to 7 days post-surgery (0-100 visual analogue scale)	Results presented graphically. Pain scores were improved with buprenorphine compared to tramadol starting 24 hours post-surgery.	High risk of selection bias. Random number table used for randomization, but allocation concealment was not reported. Baseline pain scores at rest appeared to differ between groups. High risk of performance bias due to open-label design though outcome assessors were unaware of treatment groups. High risk of reporting bias as statistical analyses and differences between groups were not reported.

Abbreviations: APAP = acetaminophen; CI = confidence interval; DB = double blind; h = hour; IV = intravenous; MC = multicenter; MD = mean difference; NI = non-inferiority; NRS = numeric rating scale; OL = open label; RCT = randomized controlled trial

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Appendix 1: Current Preferred Drug List

Substance Use Disorder, Opioid and Alcohol

Generic	Brand	Form	Route	PDL
buprenorphine	SUBLOCADE	SOLER SYR	subcutaneous	Y
buprenorphine HCl/naloxone HCl	BUPRENORPHINE-NALOXONE	FILM	sublingual	Y
buprenorphine HCl/naloxone HCl	SUBOXONE	FILM	sublingual	Y
buprenorphine HCl/naloxone HCl	BUPRENORPHINE-NALOXONE	TAB SUBL	sublingual	Y
buprenorphine HCl/naloxone HCl	SUBOXONE	TAB SUBL	sublingual	Y
buprenorphine HCl/naloxone HCl	ZUBSOLV	TAB SUBL	sublingual	Y
buprenorphine HCl	BUPRENORPHINE HCL	TAB SUBL	sublingual	V

Opioids, Long-acting

Generic	Brand	Form	PDL
fentanyl	FENTANYL	PATCH TD72	Y
morphine sulfate	MORPHINE SULFATE CR	TABLET ER	Y
morphine sulfate	MORPHINE SULFATE ER	TABLET ER	Y
morphine sulfate	MS CONTIN	TABLET ER	Y
buprenorphine	BUPRENORPHINE	PATCH TDWK	N
buprenorphine	BUTRANS	PATCH TDWK	N
buprenorphine HCl	BELBUCA	FILM	N
buprenorphine HCl	BUPRENORPHINE HCL	FILM	N
fentanyl	FENTANYL	PATCH TD72	N
hydrocodone bitartrate	HYDROCODONE BITARTRATE ER	CAP ER 12H	N
hydrocodone bitartrate	ZOHYDRO ER	CAP ER 12H	N
hydrocodone bitartrate	HYDROCODONE BITARTRATE ER	TAB ER 24H	N
hydrocodone bitartrate	HYSINGLA ER	TAB ER 24H	N
hydromorphone HCl	EXALGO	TAB ER 24H	N
hydromorphone HCl	HYDROMORPHONE ER	TAB ER 24H	N
levorphanol tartrate	LEVORPHANOL TARTRATE	TABLET	N
methadone HCl	METHADONE HCL	ORAL CONC	N
methadone HCl	METHADONE INTENSOL	ORAL CONC	N
methadone HCl	METHADOSE	ORAL CONC	N
methadone HCl	METHADONE HCL	SOLUTION	N
methadone HCl	METHADONE HCL	SYRINGE	N
methadone HCl	METHADONE HCL	TABLET	N
methadone HCl	METHADOSE	TABLET	N
methadone HCl	DISKETS	TABLET SOL	N
methadone HCl	METHADONE HCL	TABLET SOL	N
methadone HCl	METHADOSE	TABLET SOL	N

morphine sulfate	KADIAN	CAP ER PEL	N
morphine sulfate	MORPHINE SULFATE ER	CAP ER PEL	N
morphine sulfate	MORPHINE SULFATE ER	CPMP 24HR	N
oxycodone HCl	OXYCODONE HCL ER	TAB ER 12H	N
oxycodone HCl	OXYCONTIN	TAB ER 12H	N
oxycodone myristate	XTAMPZA ER	CAP SPR 12	N
oxymorphone HCl	OXYMORPHONE HCL ER	TAB ER 12H	N
tapentadol HCl	NUCYNTA ER	TAB ER 12H	N
tramadol HCl	CONZIP	CPBP 17-83	N
tramadol HCl	TRAMADOL HCL ER	CPBP 17-83	N
tramadol HCl	CONZIP	CPBP 25-75	N
tramadol HCl	TRAMADOL HCL ER	CPBP 25-75	N
tramadol HCl	TRAMADOL HCL ER	TAB ER 24H	N
tramadol HCl	ULTRAM ER	TAB ER 24H	N
tramadol HCl	TRAMADOL HCL ER	TBMP 24HR	N

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to November 11, 2022

1	exp buprenorphine/ or exp buprenorphine, naloxone drug combination/	6994
2	exp Pain/	445711
3	exp Chronic Pain/	20923
4	noncancer pain.mp.	1117
5	2 or 3 or 4	445935
6	1 and 5	1234
7	limit 6 to (english language and humans)	771
8	limit 7 to (clinical study or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or practice guideline or randomized controlled trial or "systematic review")	328

Appendix 3. Abstracts of Randomized Comparative Trials

Londhe S, Patwardhan M, Shah R, Oak M. Efficacy and Safety of Buprenorphine Transdermal Patch for Immediate Postoperative Analgesia After Total Knee Arthroplasty Surgery. *The Journal of arthroplasty.* 2020;35(6S):S178-S181.

BACKGROUND: Total knee arthroplasty (TKA) is associated with moderate-to-severe postoperative pain. Satisfactory perioperative analgesia is essential for a good and predictable surgical outcome. Effective postoperative pain control is a major challenge to the treating surgeon and his team. Old age and multiple comorbidities restrict the choice of analgesics one can offer. Transdermal buprenorphine (TDB), widely used in chronic pain management, has been rarely studied in acute postoperative setting. The purpose of this study was to compare the safety and efficacy of a TDB patch to conventional analgesics after knee arthroplasty surgery., METHODS: A prospective randomized study was conducted with 200 patients aged 60-75 years undergoing TKA surgery under neuraxial anesthesia. All patients received periarticular local anesthetic infiltration and epidural/femoral nerve block infusion for 72 hours postoperatively. Group A received the TDB patch 5 mcg applied at the end of surgery. Group B received a combination of paracetamol and tramadol. All patients received intravenous diclofenac as rescue analgesia. Pain scores at rest, on movement, and side effects, if any, were compared over 7 days using the numerical rating scale score., RESULTS: Pain scores at rest and on movement were significantly lower in group A (P values .008 and .01). Rescue analgesia requirement was also significantly less in this group. Only one patient had clinically significant respiratory depression, and 3 patients had local erythema., CONCLUSION: Our data shows that the TDB patch is more efficacious in reducing postoperative pain after TKA surgery and can be safely used with fewer systemic side effects when compared to conventional analgesics.

Lee JH, Kim J-H, Kim J-H, et al. Efficacy and Safety of Transdermal Buprenorphine versus Oral Tramadol/Acetaminophen in Patients with Persistent Postoperative Pain after Spinal Surgery. *Pain research & management.* 2017;2017:2071494.

PURPOSE: Control of persistent pain following spinal surgery is an unmet clinical need. This study compared the efficacy and safety of buprenorphine transdermal system (BTDS) to oral tramadol/acetaminophen (TA) in Korean patients with persistent, moderate pain following spinal surgery., METHODS: Open-label, interventional, randomized multicenter study. Adults with persistent postoperative pain (Numeric Rating Scale [NRS] >= 4 at 14-90 days postsurgery) were enrolled. Patients received once-weekly BTDS (n = 47; 5 mug/h titrated to 20 mug/h) or twice-daily TA (n = 40; tramadol 37.5 mg/acetaminophen 325 mg, one tablet titrated to 4 tablets) for 6 weeks. The study compared pain reduction with BTDS versus TA at week 6. Quality of life (QoL), treatment satisfaction, medication compliance, and adverse events (AEs) were assessed., FINDINGS: At week 6, both groups reported significant pain reduction (mean NRS change: BTDS -2.02; TA -2.76, both $P < 0.0001$) and improved QoL (mean EQ-5D index change: BTDS 0.10; TA 0.19, both $P < 0.05$). The BTDS group achieved better medication compliance (97.8% versus 91.0%). Incidence of AEs (26.1% versus 20.0%) and adverse drug reactions (20.3% versus 16.9%) were comparable between groups., IMPLICATIONS: For patients with persistent pain following spinal surgery, BTDS is an alternative to TA for reducing pain and supports medication compliance. This trial is registered with Clinicaltrials.gov: NCT01983111.

Kim H-J, Ahn HS, Nam Y, Chang B-S, Lee C-K, Yeom JS. Comparative study of the efficacy of transdermal buprenorphine patches and prolonged-release tramadol tablets for postoperative pain control after spinal fusion surgery: a prospective, randomized controlled non-inferiority trial. *European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society.* 2017;26(11):2961-2968.

PURPOSE: To compare the efficacy of a transdermal buprenorphine patch (5, 10, 15, and 20 mug/h) with that of oral tramadol (150, 200, 250, and 300 mg) for postoperative pain control after single level spinal fusion surgery., METHODS: The present study (ClinicalTrials.gov, number NCT02416804) was a prospective, randomized controlled non-inferiority trial designed to determine the efficacy of buprenorphine TDS for alleviating postoperative pain following patient controlled analgesia (PCA) in persons underwent a single level posterior lumbar interbody fusion surgery through 1:1 allocation. The primary outcome was the Visual Analog Pain Scale (VAS) score for postoperative back pain at 7 days after surgery. The non-inferior margin of the VAS

was set at delta = 1.5 points., RESULTS: The VAS score (primary outcome) for postoperative back pain at 7 days after surgery in the Buprenorphine group was not inferior compared to the Tramadol group. The overall changes in VAS scores for postoperative pain during follow-up assessments over a 2-week period did not differ between both groups. However, the VAS scores for postoperative pain significantly improved with time after surgery in both groups. The patterns of changes in the VAS scores for postoperative pain during the follow-up period were not significantly different between the both groups., CONCLUSIONS: The efficacy of buprenorphine TDS was not inferior to that of oral tramadol medication for alleviating postoperative pain in the subacute period from 72 h after surgery, following PCA administration. In addition, adverse events were similar between both groups.

Desai SN, Badiger SV, Tokur SB, Naik PA. Safety and efficacy of transdermal buprenorphine versus oral tramadol for the treatment of post-operative pain following surgery for fracture neck of femur: A prospective, randomised clinical study. *Indian journal of anaesthesia.* 2017;61(3):225-229.

BACKGROUND: Transdermal buprenorphine, which is used in chronic pain management, has rarely been studied for use in acute pain management. The aim of this study was to compare the safety and efficacy of transdermal buprenorphine patch to oral tramadol for post-operative analgesia, following proximal femur surgeries., METHODOLOGY: Fifty adult patients undergoing surgery for hip fracture under spinal anaesthesia were included in this study. One group (Group TDB) received transdermal buprenorphine 10 mcg/h patch applied a day before the surgery and other group received oral tramadol 50 mg three times a day for analgesia (Group OT). They were allowed to take diclofenac and paracetamol tablets for rescue analgesia. Pain scores at rest, on movement, rescue analgesic requirement and side effects were compared between the groups over 7 days. Chi-square and independent sample t-test were used for categorical and continuous variables, respectively., RESULTS: Resting pain scores and pain on movement were significantly lower in TDB Group on all 7 days starting from 24 h post-operatively. Rescue analgesic requirement was significantly lower in TDB Group compared to OT Group. All the patients needed rescue analgesic in OT Group whereas 68% of the patients needed the same in TDB Group. Incidence of vomiting was less and satisfaction scores were much higher in TDB Group as compared to OT Group (79% vs. 66%, P < 0.001)., CONCLUSION: Transdermal buprenorphine can be safely used for post-operative analgesia and is more efficacious in reducing post-operative pain after 24 hours, with fewer side effects when compared to oral tramadol.

Appendix 4: Key Inclusion Criteria

Population	Patients with acute or chronic non-cancer pain
Intervention	Buprenorphine (sublingual, buccal, subcutaneous, transdermal formulations)
Comparator	Other opioids (including different buprenorphine formulations)
Outcomes	Pain, quality of life, function, discontinuation due to adverse events, serious adverse events including death, overdose, respiratory depression, abuse/misuse, or development of substance use disorder
Setting	Outpatient setting

Appendix 5: Proposed Prior Authorization Criteria

Opioid Analgesics, Long-acting

Goals:

- Promote the well-being of OHP members and reduce risk for opioid misuse.
- Provide appropriate opioid coverage for OHP-funded conditions when there is documented sustained improvement in pain and function and routine monitoring for opioid misuse. Restrict use of long-acting opioid analgesics for conditions of the back and/or spine due to evidence of increased risk of misuse or increasing dose vs. benefit.
- Support appropriate risk mitigation strategies for patients on long-term opioid therapy.
- Promote the safe use of long-acting opioid analgesics by restricting use of high doses that have not demonstrated improved benefit and are associated with greater risk for accidental opioid overdose and death.

Length of Authorization:

- Initial: 90 days (except 12 months for end-of-life, sickle-cell disease, severe burn, or cancer-related pain)
- Renewal: Up to 12 months

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Requires a PA:

- All long-acting opioids and opioid combination products.

Note:

- Patients on palliative care with a terminal diagnosis or with cancer-related pain, or pain associated with sickle cell disease or severe burn injury are exempt from this PA.

Table 1. Daily Dose Threshold (90 Morphine Milligram Equivalents per Day) of Opioid Products.

Opioid	90 MME/day	Notes
Fentanyl (transdermal patch)	37.5 mcg/hr	Use only in opioid-tolerant patients who have been taking ≥60 MME daily for a ≥1 week. Deaths due to a fatal overdose of fentanyl have occurred when pets, children and adults were accidentally exposed to fentanyl transdermal patch. Strict adherence to the recommended handling and disposal instructions is of the utmost importance to prevent accidental exposure.)
Hydrocodone	90 mg	
Hydromorphone	22.5 mg	
Morphine	90 mg	
Oxycodone	60 mg	
Oxymorphone	30 mg	
Tapentadol	225 mg	

Tramadol	300 mg	300 mg/day is max dose and is not equivalent to 90 MME/day. Tramadol is not recommended for pediatric use as it is subject to different rates of metabolism placing certain populations at risk for overdose.
Methadone*	20 mg ***DO NOT USE unless very familiar with the complex pharmacokinetic and pharmacodynamics properties of methadone**. Methadone exhibits a non-linear relationship due to its long half-life and accumulates with chronic dosing. Methadone also has complex interactions with several other drugs. The dose should not be increased more frequently than once every 7 days. Methadone is associated with an increased incidence of prolonged QTc interval, torsades de pointe and sudden cardiac death.	

Table 2. Specific Long-acting Opioid Products Subject to Frequency Limits per FDA-approved Labeling.

Drug Product	Quantity Limit
BELBUCA	2 doses/day
BUTRANS	1 patch/7 days
EMBEDA	2 doses/day
EXALGO	1 dose/day
Fentanyl patch	1 dose/72 hr

Drug Product	Quantity Limit
HYSINGLA ER	1 doses/day
KADIAN	2 doses/day
MORPHABOND	2 doses/day
MS CONTIN	3 doses/day
NUCYNTA ER	2 doses/day
OPANA ER	2 doses/day

Drug Product	Quantity Limit
OXYCONTIN	2 doses/day
TROXYCA ER	2 doses/day
XARTEMIS XR	4 doses/day
XTAMPZA ER	2 doses/day
ZOHYDRO ER	2 doses/day

Approval Criteria		
1. What is the patient's diagnosis?	Record ICD10 code	
2. Is the patient already established on any opioid treatment for >6 weeks (long-term, chronic treatment)?	**Yes**: Go to **Renewal Criteria**	**No**: Go to #3
3. Has the patient failed to have adequate benefit with daily use of short-acting opioids? Note: long-acting opioids are not recommended as initial opioid therpay due to increased risk of death, overdose, and abuse. If trial of an opioid is necessary, short-acting opioids are recommended for initial treatment.	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.

4. Is the diagnosis funded by the OHP? Note: Management of pain associated with *back or spine conditions with long-acting opioids* is not funded by the OHP*. Other conditions, such as fibromyalgia, TMJ, neuropathy, tension headache and pelvic pain syndrome are also not funded by the OHP.	**Yes:** Go to #5	**No:** Current age ≥ 21 years: Pass to RPh. Deny; not funded by the OHP. Note: Management of opioid dependence is funded by the OHP. Age < 21. Current age < 21 years: Go to #5
5. Is there documentation that the patient has inadequate response or contraindication to all applicable pharmacologic and non-pharmacologic treatments for the requested condition? Relevant treatments may include: Pharmacologic: topical pain medications, NSAIDs, acetaminophen, or muscle relaxants. Non-pharmacologic: cognitive behavioral therapy, physical or occupational therapy, acupuncture, supervised exercise therapy, interdisciplinary rehabilitation, yoga/pilates, and chiropractic/osteopathic manipulation.	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is the requested medication a preferred agent?	**Yes:** Go to #8	**No:** Go to #7

7. Will the prescriber change to a preferred product? Note: Preferred opioids are reviewed and designated as preferred agents by the Oregon Pharmacy & Therapeutics Committee based on published medical evidence for safety and efficacy.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #8
8. Is the patient being treated for pain associated with sickle cell disease, severe burn injury, cancer-related pain or under palliative care services with a life-threatening illness or severe advanced illness expected to progress toward dying?	**Yes:** Approve for up to 12 months	**No:** Go to #9
9. Is the prescription for pain associated with migraine or other type of headache? Note: there is limited or insufficient evidence for opioid use for many pain conditions, including migraine or other types of headache.	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #10
10. Does the total daily opioid dose exceed 90 MME (see Table 1)?	**Yes:** Pass to RPh. Deny; medical appropriateness. Note: Management of opioid dependence is funded by the OHP.	**No:** Go to #11
11. Is the prescriber enrolled in the Oregon Prescription Drug Monitoring Program (www.orpdmp.com) and has the prescriber verified at least once in the past month that opioid prescribing is appropriate?	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness

12. Is the patient concurrently on other short- or long-acting opioids (patients may receive a maximum of one opioid product regardless of formulation)? Note: There is insufficient evidence for use of concurrent opioid products (e.g., long-acting opioid with short-acting opioid).	**Yes:** Pass to RPh. Deny; medical appropriateness Note: Management of opioid dependence is funded by the OHP.	**No:** Go to #13
13. Is the patient currently taking a benzodiazepine or other central nervous system (CNS) depressant? Note: All opioids have a black box warning about the risks of profound sedation, respiratory depression, coma or death associated with concomitant use of opioids with benzodiazepines or other CNS depressants.	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #14
14. Does the prescription exceed quantity limits applied in Table 2 (if applicable)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #15
15. Can the prescriber provide documentation of sustained improvement of at least 30% in pain, function, or quality of life in the past 3 months compared to baseline (e.g., prior to opioid prescribing)? Note: Pain control, quality of life, and function can be quickly assessed using the 3-item PEG scale. **	**Yes:** Go to #16 Document tool used and score vs. baseline: _____	**No:** Pass to RPh. Deny; medical appropriateness. Note: Management of opioid dependence is funded by the OHP.

16. Has the patient had a urinary drug screen (UDS) within the past 3 months to verify absence of illicit drugs and non-prescribed opioids?	**Yes:** Approve for up to 90 days.	**No:** Pass to RPh. Deny; medical appropriateness. Note: Management of opioid dependence is funded by the OHP.

Renewal Criteria		
1. What is the patient's diagnosis?	Record ICD10 code	
2. Is the request for a patient already established on opioid treatment for >6 weeks (long-term treatment)?	**Yes**: Go to #3	**No**: Go to **Approval Criteria**
3. Does the request document a taper plan for the patient?	**Yes:** Document taper plan and approve for duration of taper or 3 months whichever is less.	**No:** Go to #4
4. Is the diagnosis funded by the OHP? Note: Management of pain associated with *back or spine conditions with long-acting opioids* is not funded by the OHP*. Other conditions, such as fibromyalgia, TMJ, neuropathy, tension headache and pelvic pain syndrome are also not funded by the OHP.	**Yes:** Go to #5	**No:** Go to #6

5. Does the patient have risk factors for overdose? Risk factors may include, but are not limited to: a. Concomitant CNS depressants (i.e., benzodiazepines, muscle relaxants, sedating antipsychotics, etc.) b. Total daily opioid dose > 90 MME or exceeding quantity limits in Table 2 c. Recent urine drug screen indicating illicit or non-prescribed opioids d. Concurrent short- and long-acting opioid use e. Diagnosis of opioid use disorder f. History of opioid overdose g. Household members, including children, or other close contacts at risk for accidental ingestion or opioid overdose without documentation of secure storage mechanisms (e.g., lockbox, etc)	**Yes:** Go to #6	**No:** Go to #7
6. Is there documentation indicating it is **unsafe** to initiate a taper at this time?	**Yes:** Go to #7 Document provider attestation and rationale	**No:** Pass to RPh. Deny; medical appropriateness. May approve one time for a maximum of 1 month to allow time to document a taper plan or rationale for why a taper is unsafe at this time.

7. Is the prescriber enrolled in the Oregon Prescription Drug Monitoring Program (www.orpdmp.com) and has the prescriber verified at least once in the past 1 month that opioid prescribing is appropriate?	**Yes:** Go to #8	**No:** Pass to RPh. Deny. Medical appropriateness
8. Has the patient had a urinary drug screen (UDS) in the past 1 year and verified absence of illicit drugs and non-prescribed opioids?	**Yes:** Go to #9	**No:** Pass to RPh. Deny. Medical appropriateness
9. Can the prescriber provide documentation of sustained improvement of at least 30% in pain, function, or quality of life in the past 3 months compared to baseline (e.g., prior to opioid use)? Note: Pain control, quality of life, and function can be quickly assessed using the 3-item PEG scale. **	**Yes:** Go to #11 Document tool used and score vs. baseline: _____	**No:** Go to #10
10. Has the patient been referred for alternative non-pharmacologic modalities of pain treatment (e.g., physical therapy, supervised exercise, spinal manipulation, yoga, or acupuncture)?	**Yes:** Go to #11	**No:** Pass to RPh. Deny. Medical appropriateness.
11. Is the request for an increased cumulative dose compared to previously approved therapy or average dose in the past 6 weeks?	**Yes:** Go to #12	**No:** Go to #15
12. Does the prescription exceed quantity limits applied in Table 2 (if applicable)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #13
13. Does the total cumulative daily opioid dose exceed 90 MME (see Table 1)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #14

14. Is there documented rationale (e.g., new acute injury) to support the increase in dose?	**Yes:** Go to #15	**No:** Pass to RPh; deny; medical appropriateness
15. Has the member been prescribed or have access to naloxone?	**Yes:** Go to #16	**No:** Pass to RPh. Deny; medical appropriateness.
16. Does the patient have a pain agreement on file with the prescriber?	**Yes:** Go to #17	**No:** Pass to RPh. Deny; medical appropriateness
17. Has the provider evaluated goals of treatment within the past 3 months? Risk factors may include, but are not limited to: h. Concomitant CNS depressants (i.e., benzodiazepines, muscle relaxants, sedating antipsychotics, etc.) i. Total daily opioid dose > 90 MME or exceeding quantity limits in Table 2 j. Recent urine drug screen indicating illicit or non-prescribed opioids k. Concurrent short- and long-acting opioid use l. Diagnosis of opioid use disorder m. History of opioid overdose n. Household members, including children, or other close contacts at risk for accidental ingestion or opioid overdose without documentation of secure storage mechanisms (e.g., lockbox, etc)	**Yes:** Approval duration is based on the number of identified risk factors for overdose or length of treatment (whichever is less): Risk factors: >=1: 3 months 0: 12 months	**No:** Pass to RPh. Deny; medical appropriateness

*See Guideline Note 60 within the Prioritized List of Health Services for conditions of coverage for pain associated with back or spine conditions: http://www.oregon.gov/OHA/HPA/CSI-HERC/Pages/Prioritized-List.aspx

**The PEG is freely available to the public http://www.agencymeddirectors.wa.gov/Files/AssessmentTools/1-PEG%203%20item%20pain%20scale.pdf.

Citation of the original publication:

Krebs EE, Lorenz KA, Bair MJ, Damush TA, Wu J, Sutherland JM, Asch SM, Kroenke K. Development and initial validation of the PEG, a 3-item scale assessing pain intensity and interference. *Journal of General Internal Medicine*. 2009 Jun; 24:733-738.

Clinical Notes:

How to Discontinue Opioids.

Adapted from the following guidelines on opioid prescribing:

- The Washington State Interagency Guideline on Prescribing Opioids for Pain; Agency Medical Directors' Group, June 2015. Available at http://www.agencymeddirectors.wa.gov/Files/2015AMDGOpioidGuideline.pdf.

Selecting the optimal timing and approach to tapering depends on multiple factors. The decision to taper should be based on shared decision making between the patient and provider based on risks and benefits of therapy. Involving the patient in the decision to taper helps establish trust with the patient, ensures patient-focused tapering, incorporates the patient's values into the taper plan, provides education on the risks of opioid use, and establishes realistic goals and expectations. Avoid insisting on opioid tapering or discontinuation when opioid use may be warranted. The rate of opioid taper should be based primarily on safety considerations, and special attention is needed for patients on high dose opioids or with significant long-term use, as too rapid a taper may precipitate withdrawal symptoms or drug-seeking behavior. In addition, behavioral issues or physical withdrawal symptoms can be a major obstacle during an opioid taper. Patients who feel overwhelmed or desperate may try to convince the provider to abandon the taper. Although there are no methods for preventing behavioral issues during taper, strategies implemented at the beginning of chronic opioid therapy such as setting clear expectations, allowing for pauses during the taper, and development of an exit strategy are most likely to prevent later behavioral problems if a taper becomes necessary.

1. Consider sequential tapers for patients who are on chronic benzodiazepines and opioids. Coordinate care with other prescribers (e.g. psychiatrist) as necessary. In general, taper off opioids first, then the benzodiazepines.
2. Do not use ultra-rapid detoxification or antagonist-induced withdrawal under heavy sedation or anesthesia (e.g. naloxone or naltrexone with propofol, methohexital, ketamine or midazolam).
3. Establish an individualized rate of taper based on safety considerations and patient history. Common tapers have a dose reduction of 5% to 20% per month:
    a. Assess for substance use disorder and transition to appropriate medication assisted treatment if there is diversion or non-medical use,
    b. Rapid taper (over a 2 to 3 week period) if the patient has had a severe adverse outcome such as overdose or substance use disorder, or
    c. Slow taper for patients with no acute safety concerns. May consider starting with a taper of ≤10% of the original dose per month and assess the patient's functional and pain status at each visit.
4. Adjust the rate, intensity, and duration of the taper according to the patient's response (e.g. emergence of opioid withdrawal symptoms (see Table below)).
5. Watch for signs of unmasked mental health disorders (e.g. depression, PTSD, panic disorder) during taper, especially in patients on prolonged or high dose opioids. Consult with specialists to facilitate a safe and effective taper. Use validated tools to assess conditions.
6. Consider the following factors when making a decision to continue, pause or discontinue the taper plan:
    a. Assess the patient behaviors that may be suggestive of a substance use disorder
    b. Address increased pain with use of non-opioid pharmacological and non-pharmacological options.
    c. Evaluate patient for mental health disorders.
    d. If the dose was tapered due to safety risk, once the dose has been lowered to an acceptable level of risk with no addiction behavior(s) present, consider maintaining at the established lower dose if there is a clinically meaningful improvement in function, reduced pain and no serious adverse outcomes.
7. Do not reverse the taper; it must be unidirectional. The rate may be slowed or paused while monitoring for and managing withdrawal symptoms.
8. Increase the taper rate when opioid doses reach a low level (e.g. <15 mg/day MED), since formulations of opioids may not be available to allow smaller decreases.
9. Use non-benzodiazepine adjunctive agents to treat opioid abstinence syndrome (withdrawal) if needed. Unlike benzodiazepine withdrawal, opioid withdrawal symptoms are rarely medically serious, although they may be extremely unpleasant. Symptoms of mild opioid withdrawal may persist for 6 months after opioids have been discontinued (see Table below).
10. Refer to a crisis intervention system if a patient expresses serious suicidal ideation with plan or intent, or transfer to an emergency room where the patient can be closely monitored.

11. Do not start or resume opioids or benzodiazepines once they have been discontinued, as they may trigger drug cravings and a return to use. Counsel the patient on the increased risk of overdose with abrupt return to a previously prescribed higher dose. Provide opioid overdose education and consider offering naloxone.
12. Consider inpatient withdrawal management if the taper is poorly tolerated.

Symptoms and Treatment of Opioid Withdrawal.

Adapted from the Washington State Interagency Guideline on Prescribing Opioids for Pain; Agency Medical Directors' Group, June 2015. Available at http://www.agencymeddirectors.wa.gov/Files/2015AMDGOpioidGuideline.pdf)

Restlessness, sweating or tremors	Clonidine 0.1-0.2 mg orally every 6 hours or transdermal patch 0.1-0.2 mg weekly (If using the patch, oral medication may be needed for the first 72 hours) during taper. Monitor for significant hypotension and anticholinergic side effects.
Nausea	Anti-emetics such as ondansetron or prochlorperazine
Vomiting	Loperamide or anti-spasmodics such as dicyclomine
Muscle pain, neuropathic pain or myoclonus	NSAIDs, gabapentin or muscle relaxants such as cyclobenzaprine, tizanidine or methocarbamol
Insomnia	Sedating antidepressants (e.g. nortriptyline 25 mg at bedtime or mirtazapine 15 mg at bedtime or trazodone 50 mg at bedtime). Do not use benzodiazepines or sedative-hypnotics.

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